Bladder and Renal Cancers: Current Guideline-Based Management and Emerging Treatment Targets

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Disclosures

• I have served on advisory boards for, Genetech, Asana, Astellas, Medivation, Exelexis, Ferring, Sanofi-genzyme, Astra Zeneca, Orion, Eisai, Exelexis, and BMS
Kidney Cancer Management: Observations

• Not a rare disease, but a relatively small percent of community oncology practice
• Therapeutic advances now 12 years ago led to a paradigm shift in management
• Current therapeutic options for advanced disease remain non-curative and come with a potentially significant therapy burden
• New therapeutics have come on line with new challenges re: optimal sequence
Metastatic Renal Cell Carcinoma: Initial Therapy Considerations

• Role of cytoreductive nephrectomy
  – Adjuvant therapy?

• Initial therapy considerations
  – Sequential therapy
  – Disease assessment issues
  – QOL considerations

• New therapy options
Cytoreductive Nephrectomy: Current Status

- Debulking nephrectomy has become a standard of care in selected patients
- Combined analysis of two prospective trials demonstrated an overall survival (OS) advantage for the nephrectomy group (mean survival, 13.6 vs 7.8 months for the interferon alone arm)
Cytoreductive Nephrectomy: Current Status

• Appropriate candidates:
  – ECOG performance status of 0 or 1
  – Resectable primary tumor representing the majority of tumor
  – No evidence of rapidly progressing extra-renal disease
  – No prohibitive medical comorbidities

Cytoreductive Nephrectomy: Current Status

• Until we have data from trials using targeted agents cytoreductive nephrectomy remains a standard of care for selected patients

• Some observations:
  – Unlike biologics in which no change in renal mass was typical, a subset of pts with TKI’s will have a decrease in mass
  – Nephron sparing approaches are being tested utilizing targeted agents
ASSURE (ECOG E2805)

Stratify Risk
- Intermediate High
- Very High

Histology
- Clear cell
- Non-clear cell

Performance status
- 0 vs 1

Surgery
- Open
- Laparoscopic

Endpoints:
Disease-Free Survival
Overall Survival
Side Effects
(Including Cardiac, Fatigue)
Correlatives

Surgery

Randomize

Arm A Sunitinib
Daily 4 of 6 weeks for 9 cycles (1 yr)

Arm B Sorafenib
Twice daily for 9 cycles (1 yr)

Arm C Placebo
Daily for 1 year

Starting Dose | Sunitinib | Sorafenib
---|---|---
Original | 50 mg/day | 400 mg twice daily
Revised | 35 mg/day | 400 mg/day

Non-metastatic Kidney Cancer
Resectable Disease by scan
≥ T1bNany (resectable) M0 disease

Haas, N, et al. J Clin Oncol 33, 2015 (suppl 7; abstr 403)
Figure 2: Disease-free survival
HR=hazard ratio.

Figure 3: Overall survival
HR=hazard ratio.

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy

• 615 pts locoregional, high risk clear cell renal cancer
• Randomized to sunitinib 50 mg/day 4/2 for a year
• Primary end-point DFS

Figure 2. Disease-free Survival.

The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.
ASSURE vs S-TRAC

- Assure, more dose mods, included non clear cell
- S-TRAC tighter dose mods, only clear cell
- S-TRAC very mature study with 6.8 median follow-up
  - Given maturity of study, unlikely to demonstrate OS
Timing of Therapy for Patients with Metastatic RCC

• Current status of therapeutics
  – NO ONE IS CURED WITH METASTATIC DISEASE
  – Timing of therapy remains a clinical judgment
  – Subsets of patients (5-15%) may be followed expectantly for a period of time
    • No treatment, no side effects
### Table 3. Multivariable Analysis and Final Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimate ± SE</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPS &lt; 80%</td>
<td>0.92 ± 0.14</td>
<td>2.51</td>
<td>1.92 to 3.29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Time from diagnosis to treatment &lt; 1 year</td>
<td>0.35 ± 0.13</td>
<td>1.42</td>
<td>1.09 to 1.84</td>
<td>.0098</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; LLN</td>
<td>0.54 ± 0.14</td>
<td>1.72</td>
<td>1.31 to 2.26</td>
<td>.0001</td>
</tr>
<tr>
<td>Calcium &gt; ULN</td>
<td>0.59 ± 0.17</td>
<td>1.81</td>
<td>1.29 to 2.53</td>
<td>.0006</td>
</tr>
<tr>
<td>Neutrophil count &gt; ULN</td>
<td>0.88 ± 0.17</td>
<td>2.42</td>
<td>1.72 to 3.39</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Platelet count &gt; ULN</td>
<td>0.40 ± 0.16</td>
<td>1.49</td>
<td>1.09 to 2.03</td>
<td>.0121</td>
</tr>
</tbody>
</table>

**NOTE.** Total number of patients = 564.

Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.
Overall survival probability according to time after therapy initiation and risk group

No. of events/No. at risk
Favorable  11/133  16/110  4/62  2/22  0/3
Intermediate  61/301  50/182  17/82  2/18  0/3
Poor  94/152  19/36  1/3  0/1  0/0

Heng D Y et al. JCO 2009;27:5794-5799
### RCC (Clear Cell) Treatment Algorithm: 2016

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapy (level 1 evidence)</th>
<th>Other Options (≥ level 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated</strong></td>
<td>Good/ Intermediate risk</td>
<td>Pazopanib, Sunitinib, Bevacizumab + IFN, HD IL-2</td>
<td>Sorafenib, axitinib, Clinical trial, Observation</td>
</tr>
<tr>
<td><strong>Poor risk</strong></td>
<td></td>
<td>Temsirolimus</td>
<td>Sunitinib, Clinical trial</td>
</tr>
<tr>
<td><strong>Second-Line</strong></td>
<td></td>
<td>Nivolumab, Cabozantinib, Everolimus, Axitinib, Lenvatinib + everolimus</td>
<td>Sunitinib, Sorafenib, Pazopanib</td>
</tr>
</tbody>
</table>

*Adapted from M Atkins, ASCO 2006 & R Bukowski ASCO 2007*
## Initial Therapy: Advanced RCC (clear cell)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>N</th>
<th>ORR, %</th>
<th>PFS, Months</th>
<th>OS, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>IFN-α</td>
<td>735</td>
<td>47 vs 12 (P&lt;0.001)</td>
<td>11 vs 5 (P&lt;0.001)</td>
<td>26.4 vs 21.8 (P=0.049)</td>
</tr>
<tr>
<td>Pazopanib&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Placebo</td>
<td>435</td>
<td>30 vs 3 (P&lt;0.001)</td>
<td>9.2 vs 4.2 (P&lt;0.0001)</td>
<td>22.9 vs 20.5 (P=0.224 [1-sided])</td>
</tr>
<tr>
<td>Pazopanib&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>Sunitinib</td>
<td>1110</td>
<td>31 vs 25 (P=0.03)</td>
<td>8.4 vs 9.5 (HR=1.05)</td>
<td>28.3 vs 29.1 (P=0.24)</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>Placebo + IFN-α</td>
<td>732</td>
<td>26 vs 13 (P&lt;0.0001)</td>
<td>8.5 vs 5.2 (P&lt;0.0001)</td>
<td>18.3 vs 17.4 (P=0.069)</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Placebo + IFN-α</td>
<td>649</td>
<td>31 vs 13 (P&lt;0.001)</td>
<td>10.2 vs 5.4 (P&lt;0.001)</td>
<td>23.3 vs 21.3 (P=0.1291)</td>
</tr>
<tr>
<td>Temsirolimus&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>IFN-α</td>
<td>416</td>
<td>8.6 vs 4.8 (P=0.0001)</td>
<td>5.5 vs 3.1 (P=0.0001)</td>
<td>10.9 vs 7.3 (P=0.008)</td>
</tr>
</tbody>
</table>

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Key Eligibility Criteria
• Advanced/metastatic RCC
• Clear-cell histology
• No prior systemic therapy
• Measurable disease (RECIST 1.0)
• KPS ≥ 70
• Adequate organ function

Randomized 1:1

Pazopanib
800 mg qd
continuous dosing
Dose reductions to 600 mg or 400 mg

Sunitinib
50 mg qd
4 wk on/2 wk off
Dose reductions to 37.5 mg or 25 mg

Figure 1. Kaplan–Meier Estimates of Progression-free Survival According to Independent Review.
Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

• Objective response rate: (CR + PR)
  – Sunitinib 25%
  – Pazopanib 31%

• Median OS (not different)
  – Sunitinib 29.3 months
  – Pazopanib 28.4 months
<table>
<thead>
<tr>
<th>Chemistry labs (≥35%)</th>
<th>Pazopanib (n = 554), %</th>
<th>Sunitinib (n = 548), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Creatinine</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>60</td>
</tr>
</tbody>
</table>

Picking the Right Drug for the Right Patient

• For clear cell renal cancer, current data do not inform re: optimal initial drug selection
  – Cost, toxicity, route
  – Experience
• Don’t forget the role for selected patients for HD IL-2)
• Little guidance re: non clear cell histologies
• Sequence data emerging
  – Provides insight to issue of VEGFr vs mTor
## Second-Line Therapy Advanced RCC (clear cell)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>N</th>
<th>ORR, %</th>
<th>PFS, Months</th>
<th>OS, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VEGF Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Placebo</td>
<td>903</td>
<td>2 vs 0†</td>
<td>5.5 vs 2.8†</td>
<td>17.8 vs 15.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.44)</td>
<td>(P=0.146)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P&lt;0.000001)</td>
<td>17.8 vs 14.3§</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.029)]</td>
</tr>
<tr>
<td>Axitinib&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Sorafenib</td>
<td>723</td>
<td>23 vs 12‡</td>
<td>6.7 vs 4.7†</td>
<td>20.1 vs 19.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.0001)</td>
<td>(P=0.374)</td>
</tr>
<tr>
<td><strong>mTORi</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Everolimus&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>Placebo</td>
<td>410</td>
<td>1.0 vs 0.0†</td>
<td>4.9 vs 1.9†</td>
<td>14.8 vs 14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.001)</td>
<td>(P=0.162)</td>
</tr>
<tr>
<td>Temsirolimus&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Sorafenib</td>
<td>512</td>
<td>8.0 vs 8.0†</td>
<td>4.3 vs 3.9†</td>
<td>12.3 vs 16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.19)</td>
<td>(P=0.014)</td>
</tr>
<tr>
<td><strong>VEGF/MET/ AXL Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Everolimus</td>
<td>658</td>
<td>21 vs 5†</td>
<td>7.4 vs 3.9†</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Interim Data:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.001)</td>
<td>NR (HR=0.67), (P=0.005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.52)</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>Immuno-therapy</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Everolimus</td>
<td>821</td>
<td>25 vs 5‡</td>
<td>4.6 vs 4.4‡</td>
<td>25 vs 19.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(HR=0.88)</td>
<td>(HR=0.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.11)</td>
<td>(P=0.002)</td>
</tr>
</tbody>
</table>

Second-line Therapy

• Until most recently the most robust clinical results in VEGF-refractory RCC appear to correlate with:
  – Continued VEGF targeting
  – Potency against the VEGF receptor
• Level 1 evidence for overall survival for two agents, PFS for 1 combination
  – nivolumab, cabozantinib
  – lenvatinib/everolimus

2013
CheckMate 025: Study Design

Primary endpoint:
- OS

Secondary endpoints:
- ORR, PFS, AEs, QOL, OS by PD-L1 expression

- Previously treated mRCC
- Stratification factors:
  - Region
  - MSKCC risk group
  - Number of prior antiangiogenic therapies

- Nivolumab 3 mg/kg intravenously every 2 weeks (N=410)
- Randomization 1:1
- No cross-over allowed

- Everolimus 10 mg qd orally (N=411)
- Patients were treated until disease progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

CheckMate 025: Progression Free Survival

**Median Progression-free Survival (95% CI)**

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>4.4 (3.7-5.5)</td>
</tr>
</tbody>
</table>

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

CheckMate 025: Overall Survival

Hazard ratio, 0.73 (98.5% CI, 0.57-0.93)  
P = 0.002

No. of Patients | Median Overall Survival (95% CI) | No. of Deaths
--- | --- | ---
Nivolumab 410 | 25.0 (21.8-NE) | 183
Everolimus 411 | 19.6 (17.6-23.1) | 215

OS by MSKCC Risk Status

**Favorable**

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Months</th>
<th>Nivo</th>
<th>Evero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>137</td>
<td>133</td>
<td>122</td>
</tr>
<tr>
<td>Evero</td>
<td>145</td>
<td>142</td>
<td>123</td>
</tr>
</tbody>
</table>

- Median OS, mo (95% CI): Nivo 29.0 (26.9-NE), Evero NE (26.9-NE)
- HR (95% CI): Nivo 0.80 (0.52-1.21), Evero NE

**Intermediate**

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Months</th>
<th>Nivo</th>
<th>Evero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>193</td>
<td>167</td>
<td>141</td>
</tr>
<tr>
<td>Evero</td>
<td>192</td>
<td>151</td>
<td>118</td>
</tr>
</tbody>
</table>

- Median OS, mo (95% CI): Nivo 21.8 (18.3-NE), Evero 18.4 (16.1-23.1)
- HR (95% CI): Nivo 0.81 (0.61-1.06)

**Poor**

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Months</th>
<th>Nivo</th>
<th>Evero</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>79</td>
<td>59</td>
<td>42</td>
</tr>
<tr>
<td>Evero</td>
<td>74</td>
<td>41</td>
<td>24</td>
</tr>
</tbody>
</table>

- Median OS, mo (95% CI): Nivo 15.3 (9.6-22.4), Evero 7.9 (5.4-9.7)
- HR (95% CI): Nivo 0.48 (0.32-0.70)

CheckMate-025: Safety Overview

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n=406)</th>
<th>Everolimus (n=397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 adverse events, n (%)</td>
<td>76 (19)</td>
<td>145 (37)</td>
</tr>
<tr>
<td>Treatment related AEs leading to treatment discontinuation, n (%)</td>
<td>31 (8)</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Drug-related deaths, n</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>Treatment beyond progression^, n (%)</td>
<td>179 (44)</td>
<td>183 (46)</td>
</tr>
</tbody>
</table>

- The most common treatment-related adverse events with nivolumab:
  - Fatigue (33%)
  - Nausea (14%)
  - Pruritus (14%)

- The most common treatment-related adverse events with everolimus:
  - Fatigue (34%)
  - Stomatitis (29%)
  - Anemia (24%)

- The most common grade 3-4 adverse events:
  - For nivolumab: fatigue (10 patients, 2%)
  - For everolimus: anemia (31 patients, 8%)

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- OS, ORR

**Stratification:**
- MSKCC risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

---

**Advanced RCC (N=650)**
- Clear cell histology
- Measurable disease
- Progression on prior VEGFR-TKI within 6 months of enrollment
- No limit to the number of prior therapies
- Antibodies targeting PD-1/PD-L1 allowed
- Brain metastases allowed if treated

**Randomization 1:1**
- No cross-over allowed

**Tumor assessment**
- by RECIST 1.1 every 8 weeks

**Treatment**
- until loss of clinical benefit or intolerable toxicity

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**METEOR: Study Design**

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- OS, ORR

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Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

Figure 2. Kaplan–Meier Estimates of Progression-free Survival.
Disease progression was assessed by an independent radiology review committee.
Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

Figure 2: Kaplan-Meier plot of overall survival through Dec 31, 2015
All 658 randomly assigned patients were included in the analysis. The number of patients censored is summarised by interval. HR=hazard ratio.
### METEOR: Overview of All Grade and Grade 3-4 Adverse Events*

<table>
<thead>
<tr>
<th>Preferred Term,</th>
<th>Cabozantinib, % (N=331)</th>
<th>Everolimus, % (N=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Back pain</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

* AEs >15% cut off

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

- Lenvatinib is an oral multitarget tyrosine kinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), PDGFRα, RET, and KIT

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial

Figure 2: Kaplan-Meier estimate of progression-free survival, by treatment group

Selecting Optimal Second-Line Therapy for Advanced RCC (clear cell)

• In patients who are immunomodulatory therapy candidates, current data supports the use of nivolumab.

• For patients with prolonged response to upfront TKI or not an optimal candidate for nivolumab, axitinib or cabozantinib (if FDA approved) is a rationale choice.
Management of Advanced RCC: Current Status

- Level 1 evidence to help drive decision making for front and second line therapy is available.
- Combination IO and IO/VEGFR phase III data coming
  - Front line setting will become less uniform
- Optimal therapy for non clear cell remains undefined
• Urothelial (bladder) cancer: Really two diseases non-muscle and muscle invasive disease
• Non-muscle invasive disease rarely seen by community oncology
• Muscle invasive bladder cancer increasingly surgically managed at referral centers
• Until 2016 essentially no change in management options in 25 years, but little uptake in practice of existing level 1 evidence- neoadjuvant chemotherapy
Bladder Cancer Management: Issues/Challenges

• A nasty aggressive epithelial cancer
• “Moderately” chemotherapy responsive, but few CR’s
• Impacts an “older” patient population
• Relatively high rate of patients with compromised performance status and/or renal function
• Integration of checkpoint inhibitors into management paradigm
Initial Therapy for Muscle Invasive Bladder Cancer

• Radical cystectomy
  – Improved outcomes associated with better surgical and postoperative management
  – Survival rates unchanged as systemic spread of disease not impacted by improved surgical technology
  – Role of extended lymph node dissection
## Survival Outcomes for Contemporary Cystectomy Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>N</th>
<th>P0</th>
<th>Operative mortality</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehrborn</td>
<td>1991</td>
<td>280</td>
<td>--</td>
<td>2.1%</td>
<td>63%</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td>Pagano</td>
<td>1991</td>
<td>261</td>
<td>9%</td>
<td>1.8%</td>
<td>57%</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>Wishnow</td>
<td>1992</td>
<td>188</td>
<td>5%</td>
<td>1.1%</td>
<td>79%</td>
<td>46%</td>
<td>33%</td>
</tr>
<tr>
<td>Waehre</td>
<td>1993</td>
<td>227</td>
<td>25%</td>
<td>--</td>
<td>61%</td>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>Vieweg</td>
<td>1999</td>
<td>686</td>
<td>--</td>
<td>--</td>
<td>58%</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Stein</td>
<td>2001</td>
<td>633</td>
<td>6%</td>
<td>3%</td>
<td>72%</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>Dalbagni</td>
<td>2001</td>
<td>284</td>
<td>10.7%</td>
<td>--</td>
<td>59%</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Studer</td>
<td>2003</td>
<td>507</td>
<td>--</td>
<td>4.5%</td>
<td>74%</td>
<td>52%</td>
<td>36%</td>
</tr>
<tr>
<td>Grossman*</td>
<td>2003</td>
<td>154</td>
<td>15%</td>
<td>0.6%</td>
<td>75%</td>
<td>--</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>3220</td>
<td>12%</td>
<td>2.2%</td>
<td>66%</td>
<td>35%</td>
<td>27%</td>
</tr>
</tbody>
</table>
Results of a phase III randomized trial of synchronous chemo-radiotherapy compared to radiotherapy alone in muscle invasive bladder cancer

(BC2001 CRUK/01/004)

Nicholas James
Cancer Research UK Institute for Cancer Sciences
University of Birmingham

S. Hussain, E. Hall, P. Jenkins, J. Tremlett, C. Rawlings, C. Hendron, R. Lewis, S. Rogers, R. Huddart on behalf of the BC2001 Investigators
Chemo-radiotherapy with 5FU/MMC (n=360): 34% reduction in bladder invasive recurrence and pelvic recurrence

2-yr LRDFS

67% (95% CI: 59%, 74%) CT = 52/182
54% (95% CI: 46%, 62%) No CT = 74/178

HR = 0.66 (95% CI: 0.46, 0.95); p=0.02

James N et al, BC2001 trial
Perioperative Chemotherapy for Muscle Invasive Disease

- MRC/EORTC and SWOG Phase III trial provides level 1 evidence supporting the role of neoadjuvant cisplatin based chemotherapy
- Adjuvant studies are inadequate in terms of power/design/conduct of the trials
- There is no evidence to support non-cisplatin based neoadjuvant chemotherapy

J Clin Oncol 29:2171-7, 2011
Management of Metastatic Urothelial Cancer: Summary of Current Evidence

- Cisplatin-based combination chemotherapy provides the potential to cure in the range of 5-15%, primarily in good PS pts with low volume nodal disease.
- Non-cisplatin based chemotherapy appears to be primarily palliative, may impact slightly on PFS.
- A small group of highly selected patients may benefit from an integrated chemotherapy/surgical approach.
Second Line Chemotherapy for Advanced Urothelial Cancer

• To date no level 1 evidence supporting improvement in survival from chemotherapy

• There is no current evidence for the superiority of salvage combination chemotherapy compared to monotherapy, or precise delineation of non-cross resistant regimens
MPDL3280A (Atezolizumab) treatment leads to clinical activity in metastatic bladder cancer


<table>
<thead>
<tr>
<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><strong>n = 205</strong></td>
<td></td>
</tr>
<tr>
<td>IHC 3</td>
<td>18 (9)</td>
</tr>
<tr>
<td>IHC 2</td>
<td>37 (18)</td>
</tr>
<tr>
<td>IHC 1</td>
<td>89 (43)</td>
</tr>
<tr>
<td>IHC 0</td>
<td>61 (30)</td>
</tr>
</tbody>
</table>

- Tumour-infiltrating immune cells
- Tumour cells

Expression characteristics of bladder cancer. Integrated analysis of mRNA, miRNA and protein data led to identification of distinct subsets of urothelial carcinoma.
Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

• Multicenter, single-arm two cohort phase II trial for locally advanced/metastatic urothelial cancer progressing after previous platinum based chemotherapy

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

**Efficacy**

**Overall Survival**

- Longer OS observed in patients with higher PD-L1 IC status
- 12-mo OS compares favorably with historic estimates of \( \approx 20\% \)


---

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

- 542 platinum treated patients with advanced urothelial cancer randomized to pembrolizumab every 3 weeks vs investigator choice of docetaxel, paclitaxel or vinflunine
- Co-primary end points OS/PFS

Bellmunt, J et al. DOI: 10.1056/NEJMoa1613683 2017
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

Overall Survival
10.3 mo in P vs 7.4 mo C

Progression Free Survival

Bellmunt, J et al. DOI: 10.1056/NEJMoa1613683 2017
# Standard Therapy in Advanced Urothelial Cancer

<table>
<thead>
<tr>
<th>Setting</th>
<th>Regimen</th>
<th>Response Rate</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>Cisplatin eligible</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MVAC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>40%-50%</td>
<td>12-15 mo</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine + cisplatin&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PGC&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin ineligible</td>
<td>36%-56%</td>
<td>7-9 mo</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine + carboplatin&lt;sup&gt;4-6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Atezolizumab</em>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>15%</td>
<td>7.9 mo</td>
</tr>
<tr>
<td></td>
<td><em>Nivolumab</em>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>20%</td>
<td>8.7 mo</td>
</tr>
<tr>
<td></td>
<td><em>Pembrolizumab</em>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>21%</td>
<td>10.3 mo</td>
</tr>
<tr>
<td></td>
<td>Single-agent chemotherapy</td>
<td>~10%</td>
<td>5-8 mo</td>
</tr>
</tbody>
</table>

## PD-1/PD-L1 Antibodies in Development in Urothelial Cancer

<table>
<thead>
<tr>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
</tr>
<tr>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>MEDI 0680 (AMP-514)</td>
</tr>
<tr>
<td>REGN2810</td>
</tr>
<tr>
<td>Avelumab (MSB-0010718C)</td>
</tr>
<tr>
<td>Atezolizumab (MPDL3280A)</td>
</tr>
<tr>
<td>Durvalumab (MEDI4736)</td>
</tr>
<tr>
<td>BMS-936559</td>
</tr>
</tbody>
</table>

**PD-1**

**PD-L1**
Anti PD1 and PDL1 Therapies: Very Early Observations

- No data at this stage to differentiate anti PD1 vs PDL1
- PDL1 expression on tumor cells/immune cells, both, neither
  - Expression on primary vs. mets?
- Response rates appear to be in the 25-30% range, with some very durable
- Combination checkpoint inhibitor trials ongoing
Optimal Management of Bladder Cancer Patients

- Multidisciplinary approach
- Optimal surgical skill set required
  - Cystectomy/extended node dissection/orthotopic is a complex procedure in an aging population
- Cisplatin and carboplatin are not the same in urothelial cancer
- Level I evidence supports cisplatin-based neoadjuvant chemotherapy
- Anti PD1/PDL1 therapies pending approval will likely have impact beyond second line i.e. non-cisplatin eligible front line patients
“I told the team we could play with anybody in the country"
Shortly, I will tell them which country."
- Lou Holtz