“The following presentation should not be regarded as an endorsement of a particular product/drug/technique by the speaker. The presentation topics were assigned to the speakers by the scientific committee of the KCA, to be presented/interpreted as part of a comprehensive scientific debate. Therefore, this presentation should not be viewed/interpreted in isolation, and should be considered in context with the other presentations in the same session."
Sequencing VEGF and PD-1 Inhibition for RCC

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Associate Professor of Medicine
Director, Urologic Oncology
UAB Comprehensive Cancer Center
Birmingham, AL
Disclosures

• Advisory board: Merck, Sanofi, Bayer, Genentech, Novartis, Pfizer, Agensys, Janssen, Amgen, Astrazeneca, Argos, Eisai, Exelixis

• Research support to institution: Onyx, Bayer, Boehringer-Ingelheim, Celgene, Merck, Pfizer, Sanofi, Astellas, Exelixis, Novartis

• Speaker: NCCN/Clinical Care Options

• Author: Uptodate
First-line therapy for ccRCC

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All risk groups (few poor risk patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib vs IFN</td>
<td>750</td>
<td>11 v 5 (p&lt;0.001)</td>
<td>26.4 v 21.8 (p=0.051)</td>
<td>47 v 12 (p&lt;0.001)</td>
</tr>
<tr>
<td>Pazopanib vs Placebo</td>
<td>435</td>
<td>10.2 v 5.4 (p&lt;0.001)</td>
<td>22.9 v 20.5 (p=0.224)</td>
<td>30 v 3 (p&lt;0.001)</td>
</tr>
<tr>
<td>Bevacizumab-IFN vs. Placebo-IFN</td>
<td>649</td>
<td>10.2 v 5.4 (p&lt;0.001)</td>
<td>23.3 v 21.3 (p=0.13)</td>
<td>31 v 13 (p=0.0001)</td>
</tr>
<tr>
<td>Bevacizumab-IFN vs. IFN</td>
<td>732</td>
<td>8.5 v 5.2 (p&lt;0.001)</td>
<td>18.3 v 17.4 (p=0.069)</td>
<td>26 v 13 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus vs. IFN</td>
<td>626</td>
<td>5.5 v 3.1 (p&lt;0.001)</td>
<td>10.9 v 7.3 (p=0.008)</td>
<td>8.6 v 4.8 (p=NS)</td>
</tr>
</tbody>
</table>
Nivolumab vs. Everolimus post 1-2 VEGFi: survival

Median OS, months (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR (98.5% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>25.0 (21.7–NE)</td>
<td>0.73 (0.6–0.89)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Everolimus</td>
<td>19.6 (17.6–23.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cabozantinib vs. Everolimus post 1-2 VEGFi: Overall Survival

Hazard ratio 0.66 (95% CI 0.53-0.83), P=0.0003

<table>
<thead>
<tr>
<th></th>
<th>Median OS mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>21.4 (18.7-NE)</td>
<td>140</td>
</tr>
<tr>
<td>Everolimus</td>
<td>16.5 (14.7-18.8)</td>
<td>180</td>
</tr>
</tbody>
</table>

Lenvatinib+Everolimus vs. Everolimus vs. Lenvatinib post 1 VEGFi: PFS (randomized phase II)

**Median, mos (95% CI)**
- **Lenvatinib/Everolimus**: 14.6 (5.9–20.1)
- **Lenvatinib**: 7.4 (5.6–10.2)
- **Everolimus**: 5.5 (3.5–7.1)

Axitinib as second-line


PFS=progression-free survival. (A) all patients, (B) previous cytokine-based regimen, and (C) previous sunitinib
Everolimus post 1-2 VEGFi

## ccRCC treatment algorithm

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapies with level 1 evidence</th>
<th>Other Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good or intermediate risk</td>
<td>Sunitinib, Pazopanib, Bevacizumab+IFN</td>
<td>High dose IL-2 Observation</td>
<td></td>
</tr>
<tr>
<td>Poor risk</td>
<td>Temsirolimus</td>
<td></td>
<td>Sunitinib, Pazopanib</td>
</tr>
<tr>
<td><strong>Second Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cytokines</td>
<td>Pazopanib, Sorafenib, Axitinib</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>Prior VEGF</td>
<td>Nivolumab, Cabozantinib, Axitinib, Lenvatinib+Everolimus</td>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td>Prior mTOR</td>
<td>No data (Axitinib)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sequencing possibilities
(based on approved labels)

- Sunitinib
- Pazopanib
- Bevacizumab + IFN

- Nivolumab
- Cabozantinib
- Lenvatinib-Everolimus
- Axitinib

- Cabozantinib
- Lenvatinib-Everolimus
- Axitinib

- Nivolumab
- Cabozantinib
- Lenvatinib-Everolimus
- Axitinib

- Cabozantinib
- Lenvatinib-Everolimus
- Axitinib

- Nivolumab
When to switch therapy?

• Treat beyond RECIST progression on VEGF inhibitors?
  - Continue VEGFi if symptomatically stable indolent progressors to extract maximum mileage
  - For isolated progression in single lesion: surgery/radiosurgery with continuation of same agent
  - ?may compromise exposure to multiple lines of therapy (i.e. nivolumab and cabozantinib have been shown to prolong OS, while continuing VEGFi beyond progression has not been evaluated in a phase III trial)

• Treat until irRECIST progression on nivolumab?
  - Initial pseudoprogression and delayed response is well documented phenomenon

• Switch therapy for symptomatic progression without objective progression for either VEGFi or nivolumab
  - Increasing pain (bone metastasis), declining ECOG-PS
Using level of evidence to select second-line therapy

- Nivolumab and Cabozantinib have Level 1 evidence for OS
- Axitinib has level 1 evidence for PFS
- Lenvatinib-Everolimus has level 2 evidence for PFS (randomized phase II)
- Everolimus has level 1 evidence for PFS (but compared to placebo)
Can we use PD-L1 expression to select for second-line nivolumab?


Median OS for Nivolumab vs. Everolimus in CHECKMATE-025

≥1% PD-L1: 21.8 vs. 18.8 months

<1% PD-L1: 27.4 vs. 21.2 months

Similar results with ≥5% and <5% PD-L1 expression,

Do genomic alterations guide therapy?

Genes, Chromosomes and Cancer Volume 53, Issue 1, pages 38-51, 29 OCT 2013 DOI: 10.1002/gcc.22116

NOT VALIDATED
Proteomics (tumor and blood) are not ready for prime time

Sonpavde, Choueiri. Br J Cancer 2012
Can we select salvage therapy based on clinical factors? prognostic risk group, number of prior VEGFis, benefit from prior VEGFis


**Toni K Choueiri, ...Robert J Motzer. Lancet Oncol, Volume 17, Issue 7, 2016, 917–927**

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**Fifteenth International Kidney Cancer Symposium**

November 4-5, 2016

Marriott Miami Biscayne Bay, Miami, Florida, USA

KidneyCancer.org

www.kidneycancersymposium.com
# Can efficacy/toxicity profile help select for second-line treatment?

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Axitinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Nivolumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Cabozantinib&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Lenvatinib/eve (RP2)&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
<td>TKI refractory (72% 1 prior)</td>
<td>TKI refractory (71% 1 prior)</td>
<td>TKI refractory (100% 1 prior)</td>
<td></td>
</tr>
<tr>
<td>MSKCC risk good/int/poor risk groups</td>
<td>28 / 37 / 33</td>
<td>35 / 49 / 16</td>
<td>45 / 42 / 12</td>
<td>24 / 37 / 39</td>
</tr>
<tr>
<td>Comparator</td>
<td>Sorafenib</td>
<td>Everolimus</td>
<td>Everolimus</td>
<td>Everolimus</td>
</tr>
<tr>
<td>ORR, %</td>
<td>19%</td>
<td>22%</td>
<td>17%</td>
<td>35%</td>
</tr>
<tr>
<td>PFS, months</td>
<td>6.7</td>
<td>4.6</td>
<td>7.4</td>
<td>12.8</td>
</tr>
<tr>
<td>OS, months</td>
<td>20.1</td>
<td>25.0</td>
<td>21.4</td>
<td>25.5</td>
</tr>
<tr>
<td>Dose reductions</td>
<td>30% (37% increase)</td>
<td>n/a</td>
<td>60%</td>
<td>71%</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>7%</td>
<td>8%</td>
<td>9%</td>
<td>29%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>50% G3</td>
<td>18% G3</td>
<td>63% G3</td>
<td>57% G3</td>
</tr>
<tr>
<td></td>
<td>6% G4</td>
<td>1% G4</td>
<td>8% G4</td>
<td>14% G4</td>
</tr>
</tbody>
</table>


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www.kidneycancersymposium.com
Cabozantinib or Len-Eve as salvage therapy for more aggressive or symptomatic disease?  Extend median PFS (unlike nivolumab)


Motzer R, Lancet Oncol 2015; 1473–1482
Can site of metastasis help select for therapy

• Cabozantinib for bone-predominant metastasis?

- In a prespecified analysis in the bone-mets subgroup, marked prolongation of PFS was observed with cabozantinib (7.4 months vs. 2.7 months, HR 0.33); Overall trial HR for PFS was 0.51

- Skeletal-related events in patients who had previous events were reported in 15 of 91 patients (16%) in the cabozantinib group and in 31 of 90 patients (34%) in the everolimus group.

Can Performance status guide second-line therapy?

• Nivolumab, Cabozantinib and Everolimus phase III trials allowed KPS ≥70 (very few PS=2 patients, ~5-10%)

• Lenvatinib-Everolimus and Axitinib trials required ECOG-PS 0-1

• Given better toxicity profile for nivolumab:
  PS2 → Nivolumab
  PS 0-1 → Cabozantinib/Lenvatinib-Eve/Axitinib (reduced doses may improve feasibility in PS2 patients)
Comorbidities may dictate Choice of First Line Therapy

Against VEGF inhibitors (? Nivolumab or Everolimus first-line in such patients):
• Poorly controlled hypertension
• Recent cardiovascular event or arterial thrombosis
• CHF

Against mTOR inhibitors:
• Poor pulmonary function (COPD)
• Poorly controlled diabetes, hyperlipidemia

Against Nivolumab:
• Autoimmune disease (anecdotally tolerable if mild and controlled)
• HIV (? An issue with ongoing HAART)
• Post-organ transplant
Durable survival in phase I and II studies of salvage nivolumab for ccRCC (1-5 prior therapies)

David F. McDermott, et al, ASCO 2016

Overall Survival (Probability)

Months

Study | Median OS, months (95% CI)
--- | ---
Phase I | 22.4 (12.5–NE)
Phase II | 23.4 (17.7–26.9)
Survival by response to nivolumab in phase II study

<table>
<thead>
<tr>
<th>Response</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>NR (34.3–NE)</td>
</tr>
<tr>
<td>SD</td>
<td>22.9 (18.7–31.8)</td>
</tr>
<tr>
<td>PD</td>
<td>9.0 (5.9–14.2)</td>
</tr>
</tbody>
</table>

Overall Survival (Probability)
Patient & physician choice and financial considerations

• Oral intake vs. IV infusions (need for venous access device)

• Co-pays for oral agents (financial assistance from company)
  Len-Eve has 2 oral agents

• Physician comfort for agent

• Financial incentive to physician
Post first-line high dose IL-2

- Axitinib
- Pazopanib
- Sorafenib
- Sunitinib

(Nivolumab approved post-antiangiogenic agent therapy)
Post first-line mTOR inhibitor therapy

- Cabozantinib
- Nivolumab
- Axitinib
- Other VEGFR TKIs (sunitinib, pazopanib)
- No data for mTORi following mTORi
- Len-Eve trial excluded prior mTORi
Rechallenge

- First-line sunitinib, ≥1 different targeted therapies, and then sunitinib rechallenge.
- 52 patients
- 20%, 65%, 12%, and 4% received sunitinib rechallenge as third-, fourth-, fifth-, and sixth-line therapy, respectively
- 14.6 months (median) after stopping initial treatment.
- With first-line sunitinib and rechallenge, median PFS was 18.4 and 7.9 months, respectively
- Objective response rate was 54% and 15%.
- 2 of 8 rechallenge responders had not achieved first-line response.
- The sunitinib rechallenge safety profile was as expected, with no new adverse events reported.
- Progression with first-line sunitinib may not be associated with complete or irreversible resistance.
- Comment: In current era- ? Exhaust all known therapies known to improve OS/PFS first?
## Ongoing randomized phase III first-line trials in metastatic ccRCC

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Control arm</th>
<th>Experimental arm(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 and CTLA-4</td>
<td>Sunitinib</td>
<td>Nivolumab + Ipilimumab x 4 → Nivolumab</td>
</tr>
<tr>
<td>PD-1 and VEGF</td>
<td>Sunitinib</td>
<td>Bevacizumab + Atezolizumab</td>
</tr>
<tr>
<td>PD-L1 and VEGF</td>
<td>Sunitinib</td>
<td>Axitinib + Avelumab</td>
</tr>
<tr>
<td>VEGF/FGF and (PD1 or mTOR)</td>
<td>Sunitinib</td>
<td>Lenvatinib + Pembrolizumab OR Lenvatinib + Everolimus</td>
</tr>
<tr>
<td>Vaccine (DC+autologous tumor cell)</td>
<td>Sunitinib</td>
<td>Sunitinib + AGS-003</td>
</tr>
</tbody>
</table>
CABOSUN first-line RII trial (intermediate/poor risk only): PFS

<table>
<thead>
<tr>
<th>Arm</th>
<th>PFS Events</th>
<th>Median PFS (95% CI), mo</th>
<th>HR (95% CI)*</th>
<th>p-value (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>64</td>
<td>8.2 (6.2, 9.0)</td>
<td>0.69 (0.48-0.99)</td>
<td>0.012</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>61</td>
<td>5.6 (3.4, 8.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Table:**

<table>
<thead>
<tr>
<th>Arm</th>
<th>No. at Risk</th>
<th>Time since randomization (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>79</td>
<td>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>78</td>
<td>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30</td>
</tr>
</tbody>
</table>

**Graph:**

- **CABOSUN first-line RII trial (intermediate/poor risk only): PFS**
- **Chart:**
  - Cabozantinib vs Sunitinib
  - Median PFS:
    - Cabozantinib: 8.2 months (95% CI: 6.2, 9.0)
    - Sunitinib: 5.6 months (95% CI: 3.4, 8.1)
  - Hazard Ratio (HR): Cabozantinib vs Sunitinib
    - Cabozantinib: 0.69
    - Sunitinib: 0.48-0.99
  - p-value (one-sided): 0.012
The only trial to formally examine sequencing 
RECORD-3 RII trial (SUN→EVE vs. EVE→SUN)

Everolimus did not demonstrate noninferiority compared with sunitinib as first-line therapy (median PFS 7.9 months vs. 10.7 months, HR 1.4 (95% CI, 1.2 to 1.8).

The trial results support the paradigm of first-line sunitinib.

45% crossed over from everolimus to sunitinib, and 43% crossed over from sunitinib to everolimus

PBRM1 alteration may confer benefit from everolimus, and KDM5C to sunitinib.

Sequencing first → second line therapy in current era: From RECORD3 to SUAVE

**METASTATIC ccRCC** (untreated)

- Archival tumor (PD-L1)
- Blood (Nanostring gene expression)
- Blood (Nanostring gene expression)
- Blood (Nanostring gene expression)

**Stratification**
Prognostic risk group:
Hb, PLT, Neutrophilia, KPS<80, <1 year from diagnosis to therapy and hypercalcemia

**Primary endpoint:** Overall PFS with the sequence; Co-PIs: Sonpavde, Rini; HCRN trial
Future potential strategy for optimal sequencing of therapy for metastatic ccRCC

PS 2-3, comorbidities
- Molecular profiling
  - Single agent sunitinib
  - Molecular profiling
    - Single agent X
  - Single agent Nivolumab
  - Molecular profiling
    - Single agent Y

PS 0-1
- Combination therapy
  - PS 0-1
  - PS 2-3, comorbidities
    - Molecular profiling
      - Single agent X
      - Single agent Y

HD IL-2

Concluding remarks: sequencing of therapy for ccRCC

- Sequencing following first-line VEGFi is guided by toxicity profile, comorbidities, patient and physician preference and financial concerns

- The therapeutic landscape may evolve rapidly with emergence of combination regimens for first-line therapy
  (and ?cabozatinib as first-line therapy, i.e. ?Cabozatinib → Nivolumab → Len/Eve)

- Given difficulty of comparing the multitude of possible sequences of multiple lines of therapy, a definitive resolution to the conundrum is unlikely

- Molecular biomarkers to select for efficacy and toxicity are not ready for prime time, but will hopefully make precision medicine possible (more challenging with combination regimens)

- In absence of validated predictive biomarkers, physicians should probably attempt to deliver as many lines of therapy as possible based on approved indications (Trials should be offered for every line since cure is unlikely with current therapy).