Systemic Treatment: What Change in First Line for 2018 (beyond 2016)?

--CABOZANTINIB--

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Director, The Lank Center for Genitourinary Oncology
Co-Director, Kidney Cancer Program
President of Medical Staff
Dana-Farber Cancer Institute

Kohlberg Endowed Chair
Harvard Medical School
Outline

• Background behind the CABOSUN study
• CABOSUN Study results
• CABOSUN study in the context of other studies
• Future plans:
  – CABOSUN
  – Planned single agents studies (selected)
  – Safety of combinations with PD-1/PD-L1 inhibitors
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  – Safety of combinations with immune checkpoint blockers
Cabozantinib

- Cabozantinib is an oral small molecule inhibitor of tyrosine kinases including VEGF receptors, MET, and AXL\(^1\)

- In the randomized phase 3 METEOR trial, cabozantinib improved PFS, OS and response rate compared to everolimus in RCC patients after VEGFR TKI therapy\(^2\)
  - FDA-approved in April 2016 and EMA-approved in September 2016

- The CABOSUN study evaluated cabozantinib compared to sunitinib in previously untreated poor and intermediate risk RCC patients
  - Clinical Trials.gov identifier: NCT01835158

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\(^1\) Yakes FM et al., Mol Cancer Ther, 2011
\(^2\) Choueiri TK et al., NEJM 2015 and Lancet Oncol, 2016
IMDC Risk Groups, VEGF targeted therapy era OS

- Favorable: 43 months
- Intermediate: 23 months
- Poor: 8 months

Number at risk:
- Favourable: 157
- Intermediate: 440
- Poor: 252

Survival rates by risk group:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Favourable</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>157</td>
<td>440</td>
<td>252</td>
</tr>
<tr>
<td>12</td>
<td>109</td>
<td>247</td>
<td>65</td>
</tr>
<tr>
<td>24</td>
<td>74</td>
<td>122</td>
<td>15</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>48</td>
<td>17</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Log rank p<0.0001

Heng and Choueiri, Lancet Oncology 2013
IMDC Risk Groups, VEGF targeted therapy era OS

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- Intermediate: 23 months
- Poor: 8 months

Number at risk:
- Favorable: 157
- Intermediate: 440
- Poor: 252

Time since start of treatment (months):
- 0, 12, 24, 36, 48, 60

Overall survival (%):
- 100, 80, 60, 40, 20, 0

Log rank p < 0.0001

More urgent unmet need

Heng and Choueiri, Lancet Oncology 2013
The IMDC Intermediate/Poor risk vs. Favorable risk

• One study from the IMDC showed mPFS 5.6 months in poor/intermediate risk patients (N=1174)\(^1\)

• One prospective study of observation in mRCC showed on multivariable analysis that the number of IMDC risk factors was the only independent prognostic factor for reduced time to progression\(^2\)

1. Ko et al, BJC, 2014
Study Design (CABOSUN)

Stratification:
- IMDC risk group: intermediate, poor
- Bone metastases: yes, no

**Advanced RCC (N=150)**
- Clear cell component
- Measurable disease
- No prior systemic therapy
- ECOG PS 0-2
- IMDC intermediate or poor risk groups

Randomization 1:1
No cross-over allowed

**Primary endpoint:** PFS

**Tumor assessment** by RECIST 1.1 every other cycle

**Cabozantinib**
- 60 mg qd orally (6 week cycles)

**Sunitinib**
- 50 mg qd orally (4 weeks on/2 weeks off)

Log-rank test 85% power to detect hazard ratio = 0.67 with 1-sided type I error rate=0.1
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  – Safety of combinations with immune checkpoint blockers
  – Planned studies (selected)
# Baseline Characteristics (N=157)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cabozantinib (N=79)</th>
<th>Sunitinib (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (40-82)</td>
<td>64 (31-87)</td>
</tr>
<tr>
<td>Male, %</td>
<td>84</td>
<td>73</td>
</tr>
<tr>
<td>ECOG performance status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>IMDC risk group¹, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Poor</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Prior nephrectomy, %</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>Bone metastases, %</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>

Adverse risk factors¹: hemoglobin<LLN, cCa>ULN, KPS<80%, neutrophils>ULN, time from diagnosis to therapy <1 year, platelets>ULN

Intermediate risk group 1-2 risk factors
Poor-risk group 3 or more risk factors

¹ Heng, Xie and Choueiri et al., J Clin Oncol, 2009
Investigator-Assessed Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>PFS Events</th>
<th>Median PFS (95% CI), mo</th>
<th>HR (95% CI)*</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>
</tr>
<tr>
<td>Sunitinib</td>
<td>61</td>
<td>5.6 (3.4, 8.1)</td>
<td>p-value (one-sided) = 0.012</td>
</tr>
</tbody>
</table>

* Adjusted for bone metastases and IMDC risk groups
**PFS Subgroup Analysis**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (mo)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cabozantinib</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>15</td>
<td>8.2</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMDC Risk Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>12</td>
<td>8.4</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>30</td>
<td>6.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Bone Metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>8.7</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
<td>6.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Presented at the ESMO 2016 Congress, Copenhagen
# Tumor Response by RECIST
*(Investigator Assessment)*

<table>
<thead>
<tr>
<th></th>
<th>Cabozantinib (N=79)</th>
<th>Sunitinib (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, n (%)</strong></td>
<td>36 (46%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>34%-57%</td>
<td>10%-28%</td>
</tr>
<tr>
<td><strong>Best overall response, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>Stable disease</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Not evaluable or missing*</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>
Presented at the ESMO 2016 Congress, Copenhagen

Best Target Lesion Change from Baseline

87.3% (69/79) of cabozantinib-treated patients experienced tumor reduction

43.6% (34/78) of sunitinib-treated patients experienced tumor reduction

Not evaluated: n=3

Cabozantinib

Sunitinib

Not evaluated: n=16
Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Deaths</th>
<th>Median Survival (95% CI), mo</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>37</td>
<td>30.3 (14.6, 35.0)</td>
<td>0.80 (0.50, 1.26)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>41</td>
<td>21.8 (16.3, 27.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for bone metastases and IMDC risk group

No. at Risk
- Cabozantinib: 79, 71, 58, 35, 16, 5
- Sunitinib: 78, 60, 49, 34, 17, 4

Median F/U: 22.8 months!
# All-Causality Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term, %</th>
<th>Cabozantinib (N=78)</th>
<th>Sunitinib (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><em>Any adverse event</em></td>
<td>99</td>
<td>65</td>
</tr>
<tr>
<td>Fatigue</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>81</td>
<td>28</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>AST increased</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td><strong>ALT increased</strong></td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Anorexia</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td><strong>PPE</strong></td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>12</td>
<td>0</td>
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*Events reported in at least 30% of patients in either study group; PPE, palmar-plantar erythrodysesthesia.*
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<tr>
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<td>0</td>
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### CABOSUN vs. other contemporary 1\textsuperscript{st} line RCC studies: other adverse factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Model</th>
<th>Favorable Risk Group (%)</th>
<th>Bone mets</th>
<th>ECOG PS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABOSUN</td>
<td>IMDC</td>
<td>0</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>RECORD-3\textsuperscript{1}</td>
<td>MSKCC</td>
<td>30</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>COMPARZ\textsuperscript{2}</td>
<td>IMDC</td>
<td>25</td>
<td>18</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

1. Motzer et al. JCO 2014  
2. Motzer et al, NEJM 2013
Alliance/CALGB/Cooperative groups studies compared to Industry-based studies: lower PFS with same regimen/similar population

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>MSKCC Favorable or intermediate (%)</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVOREN¹</td>
<td>Bev + IFN-α</td>
<td>90%</td>
<td>10.2 months</td>
</tr>
<tr>
<td>CALGB²</td>
<td>Bev + IFN-α</td>
<td>90%</td>
<td>8.5 months</td>
</tr>
</tbody>
</table>

2. Rini et al, JCO 2008
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CABOSUN: what is next for that study?

• Central review of PFS and ORR
• OS update
• IHC for c-MET
  – In previously treated population (METEOR), cMET IHC was not predictive of cabozantinib activity\(^1\)

1. Powles et al, IKCS meeting, 2016
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Planned/ongoing single agent studies of Cabozantinib in RCC

• Non-clear cell RCC:
  – PAPMET: cabozantinib vs. crizotinib vs. savolitinib vs. sunitinib (SWOG, Pal) restricted to papillary RCC
  – CABOSUN-2: cabozantinib vs sunitinib (MDACC)

• Clear cell RCC (may allow non-clear cell):
  – NivoCab: cabozantinib lead-in followed by adding nivolumab (Harvard, Harshman)
  – Atezo+Cabo: (Pal): includes bladder+RCC

Search included Cancer.gov, April 20 2017
**SWOG PAPMET Study (PI: Monty Pal)**

**Advanced Papillary RCC**

mPRCC
- Histologically confirmed diagnosis of PRCC
- Measurable disease
- 0-1 prior lines of therapy
- No prior therapy with sunitinib
- Zubrod 0-1

Randomization

Primary Endpoint:
- Progression-free survival

Secondary Endpoints:
- Overall survival
- Response rate
- Adverse events
- Exploratory evaluation of:
  - MET mutational status
  - MET expression

Drugs:
- Sunitinib
- Cabozantinib
- Crizotinib
- Savolitinib
Exploration of dose and immunogenicity of NIVOllumab and CABozantinib renal cell carcinoma. (NIVOCAB)-PI: Lauren Harshman/Harvard

- Baseline pre-cabo biopsies
- Biopsies pre-adding nivolumab
- ctDNA, cfDNA, sPDL-1 (Broad, Freeman lab, Van Allen labs)
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A Phase I/Expansion Study of Cabozantinib Plus Nivolumab (CaboNivo) Alone or With Ipilimumab (CaboNivolpi) in Patients With Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

Treatment Schema and Dose Levels

**Part 1: 28-day cycle**
- **Cabozantinib**
  - PO daily
  - Continuous
- **Nivolumab**
  - IV
  - Every 2 weeks

**Part 2: 21-day cycle**
- **Cabozantinib**
  - PO daily
  - Continuous
- **Nivolumab**
  - IV
  - Every 2 weeks
- **Ipilimumab**
  - Every 3 weeks
  - x 4 doses only

Expansion cohorts:
1. Urothelial carcinoma
2. Renal cell carcinoma

Experimental Therapeutics Clinical Trials Network (ETCTN)

Apolo AB, et al. GU ASCO 2017 abstract 293
*Solid tumor in lung became cavitary (no solid component), but outline became larger; categorized as stable disease.

CRPC: castration-resistant prostate cancer; GCT: germ cell tumor; SCC: squamous cell carcinoma; urachal: urachal adenocarcinoma

Apolo AB, et al. GU ASCO 2017

Apolo AB, et al. ESMO 2016 abstract 774PD
Selected Ongoing Phase 3 Trials of Combination Therapy with Immune Checkpoint Blockers and Vaccines as First-Line Treatment for Advanced RCC.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary End Point</th>
<th>Estimated No. of Patients Enrolled</th>
<th>Trial</th>
<th>ClinicalTrials.gov No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab–lenvatinib vs. everolimus–lenvatinib vs. sunitinib</td>
<td>Progression-free survival</td>
<td>735</td>
<td>CLEAR</td>
<td>NCT02811861</td>
</tr>
<tr>
<td>Nivolumab–ipilimumab vs. sunitinib</td>
<td>Progression-free survival and overall survival</td>
<td>1070</td>
<td>CheckMate 214</td>
<td>NCT02231749</td>
</tr>
<tr>
<td>Atezolizumab–bevacizumab vs. sunitinib</td>
<td>Progression-free survival and overall survival in PD-L1–detectable tumors</td>
<td>900</td>
<td>IMmotion151</td>
<td>NCT02420821</td>
</tr>
<tr>
<td>Avelumab–axitinib vs. sunitinib</td>
<td>Progression-free survival</td>
<td>583</td>
<td>JAVELIN Renal 101</td>
<td>NCT02684006</td>
</tr>
<tr>
<td>Pembrolizumab–axitinib vs. sunitinib</td>
<td>Progression-free survival and overall survival</td>
<td>840</td>
<td>KEYNOTE-426</td>
<td>NCT02853331</td>
</tr>
<tr>
<td>Autologous dendritic-cell immunotherapy–sunitinib vs. sunitinib</td>
<td>Overall survival</td>
<td>450</td>
<td>ADAPT</td>
<td>NCT01582672</td>
</tr>
</tbody>
</table>
Exelixis and Bristol-Myers Squibb Enter Clinical Collaboration for Late-Stage Combination Trial in First-Line Renal Cell Carcinoma

- Companies intend to initiate pivotal trial evaluating CABOMETYX™ (cabozantinib) with Opdivo® (nivolumab) alone or in combination with Yervoy® (ipilimumab) in first-line renal cell carcinoma
Acknowledgements and Funding

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Lauren Harshman
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Joaquim Bellmunt
Mark Pomerantz
Craig Norton
Stats Team

Computational Team/Broad Institute
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Stephanie Mullane
Levi Garraway
Eli Van Allen

DFCI/BWH/BIDMC/Harvard
Sabina Signoretti
Bill Kaelin
Dave McDermott
K. Mahoney
M. Giannakis
David Kwiatkowski
Cathy Wu
Gordon Freeman

US and International collaborators
IMDC members
TCGA collaborators
Industry collaborators

The Patients

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1R21CA191687-01

Kidney Cancer Association
www.KidneyCancer.org
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