Metastatic Renal Cell Cancer
SIOG Position Paper

Matti Aapro
on behalf of

Joaquim Bellmunt, Sylvie Négrier,
Bernard Escudier, Ahmad Awada
Review

EORTC-GU group expert opinion on metastatic renal cell cancer

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\textsuperscript{b}Medical Oncology Service, University Hospital del Mar, Barcelona, Spain
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\textsuperscript{e}Clinique de Genolier, Genolier, Switzerland
mRCC 2008 EORTC position

clear-cell carcinomas...

• CONSIDER SURGERY OF THE PRIMARY

• CONSIDER METASTASECTOMY
FIRST-LINE THERAPY

good- or intermediate-risk metastatic RCC

- Sunitinib [Level 1b]
- Bevacizumab plus IFN-alpha [Level 1a]
- …. Sorafenib for patients ineligible for these agents [Level 2]

- High-dose IL-2 is an option for selected patients [Level 2]
FIRST-LINE THERAPY poor-prognosis metastatic RCC

- temsirolimus [Level 1b]
- sunitinib is an alternative [Level 2]
Temsirorlimus « poor-risk »
3 of 6 factors needed

- LDH level more than 1.5 times ULN
- Hb less than lower limit of normal
- Corrected serum calcium greater than 10 mg/dl (2.5 mmol/L)
- Less than 1 year from original diagnosis to development of metastatic disease;
- Karnofsky PS of 70 or less
- Metastases in more than one organ.
mRCC 2008 EORTC position
clear-cell carcinomas...

SECOND-LINE THERAPY

In cytokine refractory patients, sorafenib is recommended [Level 1b].

Everolimus is the agent of choice when patients have progressed on a tyrosine kinase inhibitor [Level 1b].
The medical treatment of metastatic renal cell cancer in the elderly: Position paper of a SIOG Taskforce

Joaquim Bellmunt\textsuperscript{a,*}, Sylvie Négrier\textsuperscript{b}, Bernard Escudier\textsuperscript{c}, Ahmad Awada\textsuperscript{d}, Matti Aapro\textsuperscript{e}

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Accepted 15 August 2008
mRCC SIOG position

• Treatments currently recommended for metastatic renal cell cancer (mRCC) have not been evaluated specifically in elderly patients.

• We considered available « age-selected » data from phase III trials of the targeted agents sorafenib (Nexavar), sunitinib (Sutent), temsirolimus (Torisel), and bevacizumab (Avastin), and from a study of expanded access to sunitinib and sorafenib.
mRCC SIOG position

• It would appear that RCC patients aged over 65 years benefit as much from these targeted therapies as younger patients and do not experience more frequent or severe toxicity.

• However, no data are available for patients aged over 85 years.
Sorafenib for Older Patients With Renal Cell Carcinoma: Subset Analysis From a Randomized Trial

Tim Eisen, Stéphane Oudard, Cezary Szczylík, Gwenaelle Gravis, Hans Heinzer, Richard Middleton, Frank Cihon, Sibyl Anderson, Sonalee Shah, Ronald Bukowski, Bernard Escudier; for the TARGET Study Group
JNCI 2008

Patients at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients at Risk</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo &lt; 70 yrs</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Placebo ≥ 70 yrs</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Sorafenib &lt; 70 yrs</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>Sorafenib ≥ 70 yrs</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

Weeks

0 50 100 150 200 250 300 350 400 450 500 550

PFS Probability

0.00 0.25 0.50 0.75 1.00

median, days (95% CI) HR (Sor/Pla) (95% CI)

Placebo < 70 yrs    83 (77, 88)    0.55 (0.47, 0.66)
Placebo ≥ 70 yrs    97 (49, 129)    0.43 (0.26, 0.69)
Sorafenib < 70 yrs  167 (159, 181) 0.55 (0.47, 0.66)
Sorafenib ≥ 70 yrs  184 (164, 280) 0.43 (0.26, 0.69)
Cardiac ischemia or infarction and left ventricular dysfunction events are of particular concern in older patients treated with anti-angiogenic and certain cytotoxic agents. Although not common, cardiac ischemia or infarction was reported in 10 (2.6%) younger sorafenib-treated patients but in only three (4.3%) older patients, and left ventricular dysfunction was observed in three younger patients but in only one older patient.
mRCC SIOG position

Toxicity of mRCC treatment and age

Even if the toxicity is no more frequent – its impact, may be greater in elderly patients

Diarrhoea and stomatitis, even low-grade, can quickly lead to dehydration.

Small degrees of additional neurotoxicity may significantly worsen disability and dependence.
mRCC SIOG position

**EFFICACY OF mRCC**

*Treatment and age*

Sunitinib and European bevacizumab/ifn studies: age makes no difference

Sorafenib study: benefit relative to placebo is greater in elderly patients

Temsrirolimus study: no definite conclusion
Abstract 278
Updated data from a phase III randomized trial of everolimus (RAD001) versus placebo in metastatic renal cell carcinoma (mRCC)

Study Design

Target
N = 362

Stratification
• Prior VEGFr-TKI: 1 or 2
• MSKCC risk group¹: favorable, intermediate, or poor

Randomization
2:1

Everolimus 10mg/day + BSC

Placebo + BSC

Upon Disease Progression

Safety Interim Analysis
Efficacy & Safety Interim Analysis
Final Analysis

Interim analyses planned after ≈ 30% and 60% of targeted 290 events

MSKCC = Memorial Sloan-Kettering Cancer Center; BSC = best supportive care.

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>277</td>
<td>139</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>61 (27-85)</td>
<td>60 (29-79)</td>
</tr>
<tr>
<td>% MSKCC risk*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable/intermediate/poor</td>
<td>29/56/14</td>
<td>28/57/15</td>
</tr>
<tr>
<td>% Prior VEGFR-TKI therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Both</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>% Other systemic therapy</td>
<td></td>
<td></td>
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<tr>
<td>Interferon</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Interleukin 2</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>


PFS by Treatment: End of Double-Blind

Central Radiology Review

- Hazard ratio = 0.33
- 95% CI [0.25, 0.43]
- Median PFS
  - Everolimus: 4.90 mo
  - Placebo: 1.87 mo
- Log rank P value < 0.001

Investigator Assessment

- Hazard ratio = 0.32
- 95% CI [0.25, 0.41]
- Median PFS
  - Everolimus: 5.49 mo
  - Placebo: 1.87 mo
- Log rank P value < 0.001

Analysis on Feb 2008 Data Cut-Off.

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Number of patients at risk

<table>
<thead>
<tr>
<th></th>
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<tr>
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<td>139</td>
</tr>
<tr>
<td>Placebo</td>
<td>139</td>
<td>62</td>
</tr>
</tbody>
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<tr>
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<td>139</td>
</tr>
<tr>
<td>Placebo</td>
<td>139</td>
<td>62</td>
</tr>
</tbody>
</table>
Phase-3 Randomized Trial of Everolimus (RAD001) vs Placebo in Metastatic Renal Cell Carcinoma


Supported by Novartis Pharmaceuticals
Progression-Free Survival by Treatment Prior Sunitinib

Central Radiology Review

Hazard Ratio = 0.34
95 % CI [0.23, 0.51]
Median PFS
Everolimus: 3.88 mo
Placebo: 1.84 mo

Log rank $P$ value <0.001

Patients at risk
Everolimus $n = 124$
Placebo $n = 60$

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>124</td>
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<tr>
<td>2</td>
<td>80</td>
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<tr>
<td>4</td>
<td>44</td>
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<td>6</td>
<td>20</td>
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<td>8</td>
<td>7</td>
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<tr>
<td>10</td>
<td>1</td>
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<td>12</td>
<td>0</td>
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<td>14</td>
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<td>4</td>
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<td>12</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>
Progression-Free Survival by Treatment Prior Sorafenib

Central Radiology Review

Hazard Ratio = 0.25
95% CI [0.16, 0.42]
Median PFS
Everolimus: 5.88 mo
Placebo: 2.83 mo
Log rank P value <0.001

Patients at risk
Everolimus  81  63  43  23  15  7  1  0
Placebo    43  23  6   3   2  0  0  0
### Selected Treatment-Related Adverse Events: End of Double-Blind

<table>
<thead>
<tr>
<th></th>
<th>Everolimus %, (n = 274)</th>
<th>Placebo %, (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>42</td>
<td>3/0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22</td>
<td>2/0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>3/0</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>1/0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>1/0</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>&lt;1/0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>17</td>
<td>1/0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13</td>
<td>&lt;1/0</td>
</tr>
<tr>
<td>Infections (total)</td>
<td>13</td>
<td>2/2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>2/0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>14</td>
<td>4/0</td>
</tr>
</tbody>
</table>

- 4 treatment-related deaths: 1 each of candidal sepsis/ARDS, sepsis, acute respiratory failure, and recurrent bronchopulmonary aspergillosis

Analysis on Feb 2008 Data Cut-Off.
Ongoing Study: Phase II Trial of Everolimus + Bevacizumab (RECORD-2)

- First-line treatment of patients with metastatic clear-cell carcinoma of the kidney
- Primary end point: Progression-free survival
- Secondary end point: Overall survival

Everolimus 10 mg/day plus Bevacizumab 10 mg/kg q 2 wk IV

IFN-α SC plus Bevacizumab 10 mg/kg q 2 wk IV

N = 360 Randomized 1:1

SC = subcutaneous; IV = intravenous; IFN-α = interferon alfa.
Planned Study: Randomized Phase II Crossover Design (RECORD-3)

- First-line treatment of patients with previously untreated mRCC
- Primary end point: Progression-free survival (part I)
- Secondary end points: Progression-free survival at the end of part II, overall survival, safety, quality of life

**Part I**
- Sunitinib 50 mg/day, 4 wk on/2 wk off
- Everolimus 10 mg/day

**Part II**
- Sunitinib 50 mg/day, 4 wk on/2 wk off
- Everolimus 10 mg/day

**Diagram:**
- Randomized 1:1
- Disease progression
- Everolimus 10 mg/day
- Sunitinib 50 mg/day, 4 wk on/2 wk off
Conclusions

- Everolimus provides significant improvement for patients with RCC after progression on VEGFR TKIs
  - Progression free survival: median 4.9 months vs 1.9 months on placebo (central review)
  - Performance status time to decline is prolonged for everolimus vs placebo
  - Patient reported outcomes favor everolimus over placebo

- Everolimus has an acceptable safety profile

- Ongoing and future trials include expanded clinical studies and biomarker development
Any attempt to generalise our conclusion that age does not decrease the likelihood of benefit from targeted agents in RCC, nor increase risk of toxicity, should be treated with caution.
mRCC 2008 EORTC position clear-cell carcinomas...

Table 1 – Levels of evidence, based on those developed by the Oxford Centre for Evidence-based Medicine.\(^\text{3}\)

<table>
<thead>
<tr>
<th>Evidence obtained from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Systematic review of randomised controlled trials (RCTs)</td>
</tr>
<tr>
<td>1b One good quality RCT</td>
</tr>
<tr>
<td>2a Systematic review of cohort studies</td>
</tr>
<tr>
<td>2b One cohort study (or poor quality RCT)</td>
</tr>
<tr>
<td>3 Systematic review of case-control studies</td>
</tr>
<tr>
<td>4 Case series</td>
</tr>
<tr>
<td>5 Expert opinion based on experience, physiology, bench research or first principles</td>
</tr>
</tbody>
</table>