Clinical Trials in non-clear cell RCC: ESPN, ASPEN and beyond

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NCCN & ESMO Guidelines

- US and EU guidelines for kidney cancer list “clinical trial” as the preferred option for patients with advanced non-clear cell RCC.
## Non-clear cell RCC clinical trials: VEGF and mTOR inhibitors: single agent Phase II data

<table>
<thead>
<tr>
<th></th>
<th>Tannir</th>
<th>Lee</th>
<th>Koh</th>
<th>Ravaud (SUPAP)</th>
<th>Escudier (RAPTOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>57</td>
<td>31</td>
<td>49</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-clear cell</td>
<td>Non-clear cell</td>
<td>Non-clear cell</td>
<td>Papillary (I:15/II:45)</td>
<td>Papillary 16/58 (25?)</td>
</tr>
<tr>
<td>Agent</td>
<td>sunitinib</td>
<td>sunitinib</td>
<td>everolimus</td>
<td>sunitinib</td>
<td>everolimus</td>
</tr>
<tr>
<td>Previously treated</td>
<td>Yes (no prior VEGF TT)</td>
<td>Yes (46% chemo/imm)</td>
<td>Yes (47% prior VEGF TT)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ORR (RECIST)</td>
<td>5%</td>
<td>36%</td>
<td>10%</td>
<td>12%</td>
<td>NA</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>2.7</td>
<td>6.4</td>
<td>5.2</td>
<td>5.6</td>
<td>7.3 (central)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>OS (months)</td>
<td>16.8</td>
<td>25.6</td>
<td>14</td>
<td>12.5</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-28 (type I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-20.3 (type II)</td>
</tr>
</tbody>
</table>

First-line PFS by Histology (RECORD-3) ASCO 2013 and JCO 2013

Clear Cell mRCC (N=290)

Non-Clear Cell mRCC (N=66)

*Please note, this is a post-hoc exploratory sub-group analysis

<table>
<thead>
<tr>
<th>Kaplan-Meier Median PFS (mo)</th>
<th>Everolimus</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>8.08</td>
<td>10.84</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>Two-sided 95% CI</td>
<td>[1.10, 1.75]</td>
<td></td>
</tr>
</tbody>
</table>

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<th>Kaplan-Meier Median PFS (mo)</th>
<th>Everolimus</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>5.09</td>
<td>7.23</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Two-sided 95% CI</td>
<td>[0.86, 2.75]</td>
<td></td>
</tr>
</tbody>
</table>
Everolimus versus Sunitinib Prospective Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma (The ESPN Trial): A Randomized Multicenter Phase 2 Trial

Nizar M. Tannir, Eric Jonasch, Emre Altinmakas, Chaan S. Ng, Wei Qiao, Pheroze Tamboli, Priya Rao, David F. McDermott, Christopher G. Wood, and Toni K. Choueiri

The University of Texas MD Anderson Cancer Center, Houston, TX; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA
**Renal Cell Carcinoma #4505 Tannir**

**Everolimus vs. sunitinib in metastatic non-clear cell RCC**

**Advanced nccRCC, including all histologies**
- ECOG PS 0-1
- No prior systemic therapy

**Primary Endpoint : PFS in first-line (1L)**

**N = 108 planned, 73 enrolled, stopped early by DSMC (at first interim analysis) due to OS favoring sunitinib**

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**Randomize**

**Everolimus 10 mg PO QD**

**Sunitinib 50 mg QD (4 wk on/2 wk off)**

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<table>
<thead>
<tr>
<th></th>
<th>Everolimus, n=35</th>
<th>Sunitinib, n=33</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR 1st line</strong></td>
<td>2.8%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>mPFS 1st line (months)</strong></td>
<td>4.1</td>
<td>6.1</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Nb of pts receiving 2nd line</strong></td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>mOS (months)</strong></td>
<td>14.9</td>
<td>16.2</td>
<td>0.18</td>
</tr>
<tr>
<td>-mOS (non-sarcomatoid), n=49</td>
<td>10.5</td>
<td>31.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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Highlights of the Day - Genitourinary (Non prostate) Cancer

T.K. Choueiri

PRESENTED AT:
### OS (Exploratory Analysis) by Histology

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Everolimus Median, mos (95% CI)</th>
<th>Sunitinib Median, mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papillary</strong></td>
<td>14.9 (7.1, 22.7) n=13</td>
<td>16.6 (5.9, NA) n=14</td>
</tr>
<tr>
<td><strong>Chromophobe</strong></td>
<td>25.1 (4.7, NA) n=6</td>
<td>31.6 (14.2, NA) n=6</td>
</tr>
<tr>
<td><strong>Unclassified</strong></td>
<td>NA n=6</td>
<td>15.4 (NA) n=4</td>
</tr>
<tr>
<td><strong>Translocation</strong></td>
<td>8.1 (5.5, 23) n=4</td>
<td>16.2 (8.8, NA) n=3</td>
</tr>
<tr>
<td><strong>Sarcomatoid w/ clear-cell</strong></td>
<td>11.1 (2.0, NA) n=6</td>
<td>7.0 (5.4, 10.4) n=6</td>
</tr>
</tbody>
</table>
Molecular Cancer Research

RNA-seq Reveals Aurora Kinase Driven-mTOR Pathway Activation in Patients with Sarcomatoid Metastatic Renal Cell Carcinoma

Sumanta K. Pal, Miaoling He, Tommy Tong, et al.

Mol Cancer Res  Published OnlineFirst September 2, 2014.
Phase II Study of Everolimus vs Sunitinib: Mixed Sub-type nccRCC (ASPEN)

Patients will be stratified by histology and MSKCC risk criteria.

Key inclusion criteria
- Papillary or chromophobe nccRCC
- KPS ≥60

Key exclusion criteria
- Collecting duct, medullary, small cell, oncocytoma, or lymphoma-type pathology
- Prior systemic therapy for mRCC

Primary end point: PFS
Secondary end points: tolerability, QoL

Treat until disease progression, unacceptable toxicity, or withdrawal of consent

n = 108

Everolimus 10 mg QD on days 1–42 of each 42-day cycle

Sunitinib 50 mg QD on days 1–28 of each 42-day cycle

This study is ongoing, but not recruiting participants.

ClinicalTrials.gov identifier: NCT01108445.
MET INHIBITORS?
Foretinib (VEGFR/MET inhibitor)

Tumor Shrinkage in 50 out of 68 patients

Germline Mutations

MET aberration (MET amplification, trisomy 7 or somatic mutation; excluding germline mutations)

Tested, but no germline mutation or MET aberrations

* Confirmed PR=13.5% (all cohort)

Choueiri et al, JCO 2013
AZD6094 (Volitinib) Scientific Background

- **Papillary renal cell cancer (PRCC)**
  - AZD6094 is a selective small molecule, highly potent inhibitor of cMet
    - AZD6094 has an IC50 of 4 nM & >650 fold selectivity demonstrated vs 265 other kinases
  - AZD6094 has shown preclinical activity as monotherapy in cell lines & xenograft models (e.g. PRCC, gastrointestinal and lung cancers)
  - Ph1 monotherapy clinical activity has been reported in PRCC patients
GU111 Trial Design (accruing)

- Phase II, open-label, single-arm
  - Patients will take AZD6094 600mg PO QD (21 day = 1 cycle)
  - Biopsy distant metastatic site highly encouraged
  - MET pathways analyses (Tumor/germline)

- Stage 1:
  - Approximately 20 patients

- Stage 2: *(will occur if ≥6 tumor responses are observed in Stage 1)*
  - Approximately 55 patients

Cancer.gov/NCT 02127710
Planned cooperative Group Trials with papillary RCC

**SWOG 14XX (PI: PAL/LARA)**

- **mPRCC**
  - Histologically confirmed diagnosis of type I PRCC
  - Measurable disease
  - 0-1 prior lines of therapy
  - No prior therapy with sunitinib
  - ECOG 0-1

- Randomization
  - VEGF-TKI
  - METi 1
  - METi 2
  - METi 3
  - METi 4
  - METi 5

**Primary Endpoint:**
- Progression-free survival

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

Courtesy of Monty Pal (SWOG)
• Erlotinib: ORR 11% (Gordon, JCO 2009)
Immune Checkpoint Blockade in non-clear cell RCC
MPDL3280A: mRCC Baseline Characteristics

Safety-evaluable population with RCC in Phase I expansion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients, N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>61 (33-81)</td>
</tr>
<tr>
<td>Male</td>
<td>77%</td>
</tr>
<tr>
<td>ECOG PS 0 / 1</td>
<td>54% / 46%</td>
</tr>
<tr>
<td>Histologic subtypes, n (%)</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>62 (90%)</td>
</tr>
<tr>
<td>Non-clear cell</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Fuhrman grade 4 or with sarcomatoid histology</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>MSKCC poor risk, n (%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Prior nephrectomy, n (%)</td>
<td>66 (96%)</td>
</tr>
<tr>
<td>Previous systemic therapies, n (%)</td>
<td>60 (87%)</td>
</tr>
<tr>
<td>Cytokine-based</td>
<td>27 (39%)</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>40 (58%)</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Lung / liver / bone / brain metastases at enrollment, n (%)</td>
<td>49 (71%) / 16 (23%) / 24 (35%) / 3 (4%)</td>
</tr>
</tbody>
</table>
MPDL3280A: Response in Patient with Sarcomatoid Variant mRCC

- 51 year old male with metastatic RCC (75% sarcomatoid variant) diagnosed Oct 2011 with T3aN2 disease s/p L nephrectomy now metastatic to lungs, skin and bone
  - Prior sunitinib, temsirolimus and XRT to T9
- Poor MSKCC risk and ECOG PS 1
- PD-L1 IHC IC positive [IC IHC 3]
- Duration of response was 76 weeks

Carolina BioOncology Institute (Powderly)
McDermott et al., 26-30 September 2014, Madrid, Spain
MPDL3280A: irRC Partial Response in Patient With Metastatic Papillary RCC

- 72 year old female with metastatic RCC oncocytic papillary RCC s/p R nephrectomy and sunitinib
- **PD-L1 [IC] IHC negative (IHC 0)**

irRC, immune-related response criteria.

Yale School of Medicine (Sznol/Herbst)

McDermott et al., 26-30 September 2014, Madrid, Spain
**PD-L1 Expression in Non-clear cell Renal Cell Carcinoma**


<table>
<thead>
<tr>
<th>POSITIVE PD-L1 by IHC</th>
<th>Tumor Tissue</th>
<th>TIMC*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NON-CLEAR CELL RCC</strong></td>
<td>11%</td>
<td>56%</td>
</tr>
<tr>
<td>-Papillary (n=50)</td>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>-Chromophobe (n=36)</td>
<td>5.6%</td>
<td>30%</td>
</tr>
<tr>
<td>-Translocation Xp11 (n=10)</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>-Collecting Duct (n=5)</td>
<td>20%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*TIMC: Tumor Infiltrating Mononuclear Cells
PD-L1 Expression in Non-ccRCC and Clinical Outcome

Overall Survival

Time to Recurrence

Choueiri et al. Ann Oncol 2014
Conclusions

- VEGF and mTOR inhibitors are options for non-clear cell RCC, although clinical trials are preferred, even for front-line therapy

- Everolimus is not superior to sunitinib

- Targeting MET remains a viable strategy in papillary RCC:
  - MET pathway analysis may select for optimal candidates
  - TCGA (KIRP) results coming soon

- Immune checkpoint blockers should be tested in all RCC subtypes
Acknowledgements (Partial)
Kidney Cancer Research at DF/HCC

- BWH/DFCI/Broad/MIT: Signoretti, Freedman, Freeman, Meyerson, Garraway, Chang (Urology), Hirsch, Hodi, Kaelin…
- BIDMC and MGH: McDermott, Bhatt, Mier, Michaelson…
- Harvard School of Public Health
- DF/HCC Kidney SPORE
- Collaborators:
  - National: CCF (Rini), Mayo (Ho), COH (Pal), MSKCC (Motzer, Hakimi, Hsieh), MDACC (Tannir), Georgetown (Atkins), **IMDC Centers PIs**…
  - International: Heng/Tom Baker, Canadian Centers, **IMDC Centers**, Gustave-Roussy…
  - Industry Partners