Treatment of Non-Clear Cell Kidney Cancer

Past, Present, and Future

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Penn Medicine
Histologic Classification of Renal Cell Carcinoma

Non-clear cell Kidney Cancers:

- 15 – 20% of all kidney cancers
- Major types of Non-Clear Cell RCC:
  - Papillary type 1 and type 2
  - Chromophobe
  - Unclassified
- Several additional less common subtypes
- Sarcomatoid – admixed with any RCC subtype

Our understanding of the treatment of Non-Clear Cell RCC is evolving.

Single uniform entity → spectrum of different diseases:
- distinctive molecular and genetic alterations
- differing clinical courses
- variable responses to treatment
Treatment of Non-Clear Cell RCC: the PAST

Majority of initial studies for the treatment of RCC evaluated agents for Clear Cell Disease (80% of patients).

Little consensus regarding best practice for treatment of Non Clear Cell Disease (~20% of patients).

<table>
<thead>
<tr>
<th>FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td>Favorable(^a)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Poor/intermediate(^a)</td>
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</tbody>
</table>
Majority of initial studies for the treatment of RCC evaluated agents for Clear Cell Disease (80% of patients).

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<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Other recommended regimens</th>
<th>Useful under certain circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>Cabozantinib</td>
<td>Axitinib</td>
</tr>
</tbody>
</table>
| Sunitinib                   | Everolimus                               | Bevacizumab or biosimilar\^\^\^\^
|                             |                                          | Erlotinib                                                                                           |
|                             |                                          | Lenvatinib + everolimus                                                                             |
|                             |                                          | Nivolumab                                                                                          |
|                             |                                          | Pazopanib                                                                                          |
|                             |                                          | Bevacizumab or biosimilar\^\^\^\^ + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) |
|                             |                                          | Bevacizumab or biosimilar\^\^\^ + everolimus                                                      |
|                             |                                          | Temsirolimus\^\^\^ (category 1 for poor-prognosis risk group; category 2A for other risk groups)  |
Treatment of Non-Clear Cell RCC: the PAST

Two trials evaluated systemic treatments specifically in Non Clear Cell Disease.
Head to Head comparison: Sunitinib versus Everolimus

ESPN Trial (68 patients)

ASPEN Trial (108 patients)

Conclusion: VEGF-directed therapies are the ‘standard’ treatment for Non Clear Cell Disease (but with very modest clinical outcomes)
Non-clear cell RCC is a heterogeneous disease group
- SPLITTERS (not LUMPERS)

Each subtype bears a distinct biology

Improved understanding of the molecular underpinnings of each subtype

Defining characteristics based on chromosomal alterations, tumor metabolism, etc.
Treatment of Non-Clear Cell RCC: the PRESENT

The Cancer Genome Atlas
Collaborative project to create comprehensive “maps” of the key genomic changes in various cancers

The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma
The Cancer Genome Atlas
Collaborative project to create comprehensive “maps” of the key genomic changes in various cancers

Clear Cell RCC
- Inactivation of VHL
- Mutations in chromatin remodeling pathways (PBRM1, SETD2, BAP1)
- Mutations in PI3K-Akt-mTOR pathway
- Loss of CDKN2A

Papillary RCC
Type 1
- Activating mutations, copy number alterations MET protooncogene

Type 2
- NRF2-ARM
- NF2, SMARCB1
- Loss of CDKN2A
- MET mutation

Chromophobe RCC
- Alterations in TERT promoter region
- Mitochondrial function
- TP53, PTEN mutations
- Loss of CDKN2A
- Mutations in PI3K-Akt-mTOR pathway
Treatment of Non-Clear Cell RCC: the FUTURE

Change in Treatment Paradigm:

Extrapolating from Clear Cell RCC

Biology-Driven Clinical Trials for Specific Non-Clear Cell RCC Subtypes

Challenges with accruing patients for uncommon kidney cancers

Benefit of uniform biology to test rationale treatment strategies
Treatment of Non-Clear Cell RCC: the FUTURE

Papillary RCC
Type 1
Type 2

Sunitinib
Cabozantinib
Savolitinib
Crizotinib

Targeting MET activation
Treatment of Non-Clear Cell RCC: the FUTURE

Immune Checkpoint Inhibitors:

KEYNOTE-427: (NCT02853344)

Presented By David McDermott at 2019 Genitourinary Cancers Symposium

Patients
- Recurrent or advanced/metastatic disease
- Measurable per RECIST v1.1
- No prior systemic therapy
- Karnofsky performance status ≥70%

Cohort A
clear cell RCC
(N = 110)

Cohort B
nccRCC*
(N = 165)

Screen for eligibility

Pembrolizumab
200 mg Q3W

Response assessed at week 12 and Q6W until week 54, and Q12W thereafter

Endpoints
- Primary: ORR per RECIST v1.1 (blinded independent central review)
- Secondary: DOR, DCR, PFS, OS, safety, and tolerability
- Exploratory: ORR by histology (blinded independent central review) and PD-L1 expression: a tissue-based biomarkers (eg, IHC, RNA sequencing)

*nccRCC diagnosis confirmed by central pathology

*PD-L1 positive defined as combined positive score (CPS) ≥1.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>62 (22-86)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>59 (36)</td>
</tr>
<tr>
<td>Men</td>
<td>109 (66)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>145 (88)</td>
</tr>
<tr>
<td>Asian</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Karnofsky performance scale</td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>124 (75)</td>
</tr>
<tr>
<td>70-80</td>
<td>41 (25)</td>
</tr>
</tbody>
</table>

### Confirmed RCC histology

- Papillary: 118 (71)
- Chromophobe: 21 (13)
- Unclassified: 26 (16)

### IMDC risk category

- Favorable: 53 (32)
- Intermediate/poor: 112 (68)

### PD-L1 status

- CPS ≥1: 102 (62)
- CPS <1: 58 (35)
- Missing: 5 (3)

## ORR by Confirmed RCC Histology per Blinded Independent Central Review

<table>
<thead>
<tr>
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<th>Papillary n = 118</th>
<th>Chromophobe n = 21</th>
<th>Unclassified n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, % (95%CI)</strong></td>
<td>25.4 (17.9-34.3)</td>
<td>9.5 (1.2-30.4)</td>
<td>34.6 (17.2-55.7)</td>
</tr>
<tr>
<td><strong>DCR, % (95%CI)a</strong></td>
<td>43.2 (34.1-52.7)</td>
<td>33.3 (14.6-57.0)</td>
<td>34.6 (17.2-55.7)</td>
</tr>
<tr>
<td><strong>Confirmed BOR, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4.2</td>
<td>4.8</td>
<td>7.7</td>
</tr>
<tr>
<td>PR</td>
<td>21.2</td>
<td>4.8</td>
<td>26.9</td>
</tr>
<tr>
<td>SD</td>
<td>34.7</td>
<td>47.6</td>
<td>7.7</td>
</tr>
<tr>
<td>PD</td>
<td>33.9</td>
<td>42.9</td>
<td>46.2</td>
</tr>
<tr>
<td>No assessmentb</td>
<td>5.1</td>
<td>0.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Not evaluablec</td>
<td>0.8</td>
<td>0.0</td>
<td>3.8</td>
</tr>
</tbody>
</table>

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aDCR = CR + PR + SD ≥ 6 months. bIncludes patients who discontinued or died before first postbaseline scan. cIncludes patients with insufficient data for response assessment. Database cutoff: September 7, 2018.
Maximum Change From Baseline in Target Lesions by Central Review

- 91/165 (55.2%) experienced a reduction in tumor burden
- 20/165 (12.1%) experienced a tumor burden reduction $\geq 80\%$
- 7/165 (4.2%) experienced 100% tumor burden reduction

Includes patients who received $\geq 1$ dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and had a postbaseline assessment ($n = 155$).

*Patient had an increase in target lesions above 100%.

Treatment of Non-Clear Cell RCC: the FUTURE

Immune Checkpoint Inhibitors: Sarcomatoid RCC

[Graph showing the best reduction from baseline in target lesion (%)]

- NIVO+IPI
- SUN

* = responders
Treatment of Non-Clear Cell RCC: the FUTURE

Immune Checkpoint Inhibitors: Sarcomatoid RCC

**OS: Intermediate/Poor-Risk Sarcomatoid Patients**

<table>
<thead>
<tr>
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<th>NIVO+IPI (N = 60)</th>
<th>SUN (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>31 (52)</td>
<td>39 (75)</td>
</tr>
<tr>
<td>Median OS, (95% CI), mo</td>
<td>31.2 (23.0–NE)</td>
<td>13.6 (7.7–20.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.55 (0.33–0.90)</td>
<td>0.0155</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>NIVO+IPI</th>
<th>60</th>
<th>56</th>
<th>52</th>
<th>49</th>
<th>47</th>
<th>45</th>
<th>43</th>
<th>37</th>
<th>32</th>
<th>30</th>
<th>29</th>
<th>22</th>
<th>10</th>
<th>5</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUN</td>
<td>52</td>
<td>48</td>
<td>36</td>
<td>32</td>
<td>29</td>
<td>23</td>
<td>22</td>
<td>19</td>
<td>18</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
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</table>
• Our understanding of non-clear cell RCC is evolving

• Non-clear cell RCC represents unique subtypes with distinct molecular alterations and clinical courses
  - We are now understanding the areas of overlap and difference with conventional clear cell RCC

• Ongoing and Future Studies will evaluate treatment strategies targeting the unique biology of each subtype