Papillary Renal Cell Carcinoma
(pRCC)

Laurence Albiges, MD, PhD
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pRCC is a heterogeneous entity

Balint, 2009
Toward pRCC remodeling

New entity characterization by pathologists

Proposed new Renal Epitelial Tumors

Adapted from ISUP classification, Delahunt et al. *Urology* 2014
The International Society of Urological Pathology (ISUP)
Vancouver Classification of Renal Neoplasia

Renal cell tumors

Clear cell renal cell carcinoma
Multilocular cystic clear cell renal cell neoplasm of low malignant
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic chromophobe tumor*
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
MitT family translocation renal cell carcinoma*
Xp11 translocation renal cell carcinoma
(t6;11) renal cell carcinoma*
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma*
Acquired cystic disease associated renal cell carcinoma*
Clear cell (tubulo) papillary renal cell carcinoma*
Hereditary leiomyomatosis renal cell carcinoma syndrome-associated renal cell carcinoma*
Renal cell carcinoma, unclassified

• Prognosis ?
• Systemic therapy?
• Molecular characterisation?
Prognosis

Metastatic pRCC prognosis < ccRCC

LOCALIZED  ≠  METASTATIC

Cancer Specific Survival

pRCC > ccRCC

Steffens, EJC 2012

Cancer Specific Survival

pRCC (n=565) and cRCC (n=4376)
## Prognosis

Metastatic pRCC prognosis $< \text{ccRC}$

![Graph depicting survival probability over time for different subtypes of RCC.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n</th>
<th>ORR (CR+PR)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ccRCC</td>
<td>1963</td>
<td>27.9%</td>
<td>(20.7-23.3)</td>
</tr>
<tr>
<td>pRCC</td>
<td>151</td>
<td>14%</td>
<td>(10.9-17.1)</td>
</tr>
<tr>
<td>chRCC</td>
<td>37</td>
<td>22.9%</td>
<td>(12.6-75.3)</td>
</tr>
<tr>
<td>unclRCC</td>
<td>34</td>
<td>28%</td>
<td>(5.1-13.2)</td>
</tr>
</tbody>
</table>

Kroeger, IMDC. *Cancer* 2013
Systemic therapies pRCC

- No efficacy of cytokines or chemotherapy
- Retrospective dataset and EAP
- nonccRCC phase II (pRCC~20pts)

- Specific TT trials
  - 2 dedicated phase II first line
    - SUPAP
    - RAPTOR
  - 2 dedicated phase II beyond first line
    - Erlotinib (EGFRi)
    - Foretinib (dual VEGFR/METi)

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Ronen, Cancer, 2006
Bylow, Clin Genit Can, 2009
Choueiri, J Clin Oncol, 2009
Gore Lancet Oncol 2009
Beck, Ann Oncol, 2011
**SUPAPRATOR**

**Type 1: n = 15**

- Locally advanced or metastatic, type 1 or 2 pRCC
- No prior systemic therapy

**Non-type 1: n = 46**

Primary end points: ORR  
Secondary end points: safety, OS, PFS, time to response, duration of response

**Sunitinib 50 mg/d**

4 wk on/2 wk off

Disease progression or unacceptable toxicity

Ravaud A et al. ESMO 2012 abstract 797PD.

**Type 1 or 2 pRCC**

- Metastatic type 1 or 2  pRCC
- No prior systemic therapy

**N = 92**

Primary end points: 6 months PFS rate  
Secondary end points: DCR, ORR, duration of response, median PFS, safety

**Everolimus 10 mg/d**

Disease progression or unacceptable toxicity

Escudier B et al. ESMO 2012 abstract 798PD.
<table>
<thead>
<tr>
<th>n</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
<th>OS type I n=15</th>
<th>OS type II n=45</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>12%</td>
<td>5.6mo</td>
<td>12.5 mo (8.2-17.8 mo)</td>
<td>17.8 mo (5.7-26.1 mo)</td>
<td>12.4 mo (8.2-16.0 mo)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
<th>OS type I n=16</th>
<th>OS type II n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>NR</td>
<td>3.7 mo (2.5-5.5)</td>
<td>21 mo (15.4-28.0)</td>
<td>28.0 mo</td>
<td>20.3 mo</td>
</tr>
</tbody>
</table>

Ravaud A et al. ESMO 2012 abstract 797PD.

Escudier B et al. ESMO 2012:abstract 798PD/ ESMO 2013
EGFR inhibition in PRCC: SWOG S0317

Rational:
- EGFR overexpression in pRCC
- Pré-clinical activity

Erlotinib 150 mg per day
Continuous (28-day) cycle
n = 45

- Disease progression
- Patient refusal
- Unacceptable toxicity
- Treatment delays >3 wk

Hypothesis: If RR≥20% = Promising

No correlation with EGFR expression

### Efficacy

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<table>
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<tbody>
<tr>
<td>ORR</td>
<td>11% (95% CI, 3–24)</td>
</tr>
<tr>
<td>SD</td>
<td>53%</td>
</tr>
<tr>
<td>6-mo PFS</td>
<td>29% (95% CI, 17–42)</td>
</tr>
<tr>
<td>mOS</td>
<td>27 months (95% CI, 13–36)</td>
</tr>
</tbody>
</table>
**MET inhibition in pRCC**

- Rational
  - Protein over expression in pRCC (*Choi 2006, Gibney, 2012*)
  - MET germline and somatic mutation (*Schmidt, 1997, 2000*)

- Foretinib (VEGFR2 & MET TKI) trial
  - Population: 65 metastatic pRCC type I & II
  - Median PFS >9 months in pretreated patients, OS: 70% at 1 year
  - Germline MET mutation predictive of response

*Choueiri, JCO 2013*
Objective: Characterise c-MET distinct alteration across pRCC subtypes
1- mRNA : expression level of MET

- c-MET expression level was high across all pRCC when compared to clear cell carcinomas when compared to normal kidney expression
2- Mutation analysis

11 mutations in exons 16-19 of the MET gene were identified amongst 51 type I pRCC (21.5%) :

- 7 previously reported, including 4 times the same M1268T mutation
- 2 mutations on known sites with new AA substitution
- 2 new mutations strongly predicted to be damaging

4 new mutations:

- ✓ In silico prediction models: damaging
- ✓ Pathway analysis
Copy Number Alterations (partial gain or Kr 7 polysomy) were identified by CGHa in 46% of type II pRCC and by CGMA in 81% of type I pRCC.

Correlation between DNA copy number alterations (CGH) and mRNA expression level was highly significant.
Two MET fusions:
- BAIAP2L1–MET
- C8orf34–MET

act as dimerization motifs => potentially activates MET

MET activation in pRCC

• Associated with type I

• Distinct alterations involving MET in pRCC
  – Germline mutation TK domain
  – Somatic mutation TK domain
  – Copy Number Alteration
  – Fusion
  – ...

• Ongoing multiple MET-i trials in pRCC
  – SWOG (Dr Pal), CREATE (EORTC), ...
  – correlated response with MET alteration
Gene expression profiling identified two distinct subgroups of type II pRCC with distinct pathological features.

**CDKN2A** = *P16* (located in 9p21) loss
- was more likely to be observed in high grade tumor group 19% vs. 8%
- in line with previous report of 9p loss to be associated with a dismal prognosis in pRCC
Toward pRCC remodeling

A comprehensive molecular evaluation
to characterise underlying biology & identify therapeutic target

The Cancer Genome Atlas
Kidney Cancer Papillary (KIRP) Working Group
• Bernard Escudier
• Jean-Jacques Patard
• Salem Chouaib
  • Audrey Le Formal
  • Sophie Gad
• IGR Plateforms
  • Justine Guegan
  • Nathalie Auger
• Toni Choueiri
• Andre Fay
• Marina Kaymakcalan
• Sabina Signoretti
• Ingrid Carvo
• Rana McKay
• Broad Institute
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