Biomarkers for Targeted Therapy in RCC: Any Progress?

James J. Hsieh, MD PhD
Medicine, GU Oncology
Memorial Sloan Kettering Cancer Center
Kidney Cancer Care
Before 2005, The Dark Age
Survival With Chemotherapy and Cytokines: Retrospective MSK Experience

Tick mark (I) indicates last follow-up

Proportion Surviving

Years Following Systemic Therapy

Cytokine therapy (396 patients, 48 alive)
- Interferon-α: 294 patients
- Interleukin-2: 68 patients
- Both: 34 patients

Chemotherapy (274 patients, 9 alive)

Interferon Response rate = 12%
Median PFS to Interferon = 4.7 months

Histological Subtypes of Kidney Cancer

- **Clear Cell 70-75% (VHL)** Proximal Nephron
- **Papillary Type I 5-10% (MET)** Proximal Nephron
- **Papillary Type II 5-10%** Proximal Nephron
- **Chromophobe ~5%** Chr (1,2,6,10,13,17) Distal Nephron
- **Xp11.2 TFE3 (<1%)**
- **Medullary (SMARCB1) (<1%)**
- **Collecting Duct (<1%)**

**Unclassified 5-10% (Heterogeneous)**

Others: SDHB, FH, TSC1/2, BHD, ccPAP, TCEB1B etc.

Hsieh & Tickoo
Current Signaling Targets in ccRCC (8 approved, 1 coming)

Tumor Cell

RAS
→ RAF
→ MEK
→ MAPK

PI3K
→ AKT
→ PTEN

MEK
→ TSC1/2
→ Rheb

mTORC1
→ S6K
→ 4EBP1
→ mTORC2
→ HIF-1/2a

Endothelial Cell

HIF-1/2a
→ VHL
→ HIF-1/2α
→ TSC1/2
→ Rheb

Angiogenesis

TIE2
→ FGF
→ FGF2

MET
→ PDGF
→ PDGFR
→ VEGF
→ VEGFR

Everolimus, Temsirolimus

Bevacizumab

Sunitinib, Sorafenib, Pazopanib, Axitinib

FGFR
→ Cabozantinib
→ Lenzatinib

Nucleus

HIF1/2 Target Genes

mTORC2
→ S6K
→ 4EBP1
→ Rheb

VHL
→ VHL
Treatment for ccRCC (Past, Now & Future)

High dose interleukin-2
Interferon-α
Sorafenib
Sunitinib
Temsirolimus
Everolimus
Bevacizumab + IFN
Pazopanib
Axitinib
Nivolumab
Cabozantinib

1992-2005
2005
2006
2007
2008
2009
2010
2012
2013-2015
2016

Dark Age
Modern Age
Golden Age

Targeted Therapy 2005-2015

Hsieh, April, 2016
Pan-Omics of Three Major Kidney Cancer Types

Creighton et al. Cell Reports 2016
A Clear Picture of Clear Cell Renal Cell Carcinoma (Stage I ~ IV) (A Disease of Loss of 3p TSGs)

Hakimi et al. EU 2013, Nat Gen 2013
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Swanton et al. NEJM 2012; NG 2014
Therapeutic Responses & Genomics

Correlations between Gene Mutations and Outcomes of Targeted Therapy (VEGF & mTORC1 Inhibitors) of Patients With Metastatic Clear Cell Renal Cell Carcinoma.
### The MSKCC mTOR Inhibitor Cohort

#### 298 Cases:
- 128 Everolimus; 170 Temsirolimus

- Remove patients receiving combination therapies

#### 265 Cases:
- 100 everolimus; 165 temsirolimus

- Treatment duration ≥20 months
  - 14 cases: 7 Everolimus; 7 Temsirolimus

- Remove patients without research consent to tissue procurement

#### 13 Cases:
- 6 Everolimus; 7 Temsirolimus

- Remove patients without tissue specimens available for analysis

#### 6 cases:
- 2 Everolimus; 4 Temsirolimus

---

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age</th>
<th>Histologic subtype</th>
<th>MSKCC risk score</th>
<th>Number of prior regimens</th>
<th>Duration prior treatment with VEGF targeted therapy [months] (agent)</th>
<th># of metastatic sites</th>
<th>Rapalog</th>
<th>Best Response (RECIST 1.1)</th>
<th>Duration treatment with rapalog [months]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>58</td>
<td>clear</td>
<td>Int</td>
<td>1</td>
<td>(4 (sunitinib))</td>
<td>≥3</td>
<td>temsirolimus</td>
<td>SD</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>73</td>
<td>unclassified</td>
<td>Int</td>
<td>1</td>
<td>3 (sunitinib)</td>
<td>1</td>
<td>temsirolimus</td>
<td>PR</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>16</td>
<td>unclassified</td>
<td>Int</td>
<td>3</td>
<td>19 (sunitinib)</td>
<td>1</td>
<td>everolimus</td>
<td>PR</td>
<td>43+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>66</td>
<td>clear</td>
<td>Int</td>
<td>2</td>
<td>5 (sunitinib)</td>
<td>≥3</td>
<td>everolimus</td>
<td>SD</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>60</td>
<td>clear</td>
<td>Fav</td>
<td>3</td>
<td>11 (sunitinib)</td>
<td>≥3</td>
<td>temsirolimus</td>
<td>SD</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>50</td>
<td>unclassified</td>
<td>Fav</td>
<td>1</td>
<td>2 (sunitinib)</td>
<td>≥3</td>
<td>temsirolimus</td>
<td>SD</td>
<td>40+</td>
</tr>
</tbody>
</table>

Voss et al. CCR 2014
Mutations in TSC1, TSC2, and MTOR are associated with response to rapalogs in patients with metastatic Renal Cell Carcinoma.


Now & Near Future: Omics-Based Precision Therapy

Immunotherapy

Overcome Resistance (Multipharmacy)
## PBRM1: The Second Most Commonly Mutated Gene in Human ccRCC

### Mammalian SWI/SNF complex (mBAF)

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARID1A</td>
<td>Ovarian, hepatocellular, bladder, gastric, endometrioid, pancreatic, colon, lung, neuroblastoma, Burkitt lymphoma</td>
</tr>
<tr>
<td>ARID1B</td>
<td>Melanoma, neuroblastoma, hepatocellular, pancreatic, liver</td>
</tr>
<tr>
<td>PBRM1</td>
<td>Renal cell carcinoma, breast, gastric, pancreatic</td>
</tr>
<tr>
<td>ARID2</td>
<td>Melanoma, hepatocellular, pancreatic</td>
</tr>
<tr>
<td>SMARCA2</td>
<td>Lung, colon, breast</td>
</tr>
<tr>
<td>SMARCA4</td>
<td>Lung, medulloblastoma, Burkitt lymphoma, SCCOHT</td>
</tr>
<tr>
<td>SMARCB1</td>
<td>Rhabdoid tumor, familial schwannomatosis</td>
</tr>
<tr>
<td>SMARCE1</td>
<td>Spinal meningioma</td>
</tr>
<tr>
<td>BRD7</td>
<td>Breast</td>
</tr>
</tbody>
</table>

Nucleosome remodeling (ATPase activity)
Regulation of transcription (Transcription factor, co-activator, and co-repressor recruitment)

---

*Cancer Cell. 2014 Sep 8;26(3):309-17*
Loss of Vhl and Pbrm1 in mouse kidney causes polycystic kidney disease and early mortality.
Ksp;Vhl-/-;Pbrm1-/- mice develop multifocal clear cell kidney cancer
PBRM1 functions like an electrical resistor in restraining the transcription of HIF and STAT target genes when VHL is lost.
Convergence on the mTOR pathway activation among ccRCC from mouse $Ksp;Vhl^{F/F};Pbrm1^{F/F}$ mouse $Hif1$-TRACK, and human $VHL/PBRM1$ mutants.
Three distinct genetic/epigenetic events in the development of ccRCC.

- Loss of function
- Activation
- Positive regulation
- Negative regulation

Diagram showing relationships between VHL, HIF, STAT, PBRM1, mTOR, and ccRCC.
RECORD-3 (Whole 471 & NGS ccRCC 220)

OS, overall survival; PFS, progression-free survival. 85% ccRCC


--

Study endpoints

Primary
- PFS – 1st-line noninferiority of everolimus to sunitinib

Key Secondary
- PFS – combined
- OS (E-S 22.4 months; S-E 29.5 months)
- Safety

Primary endpoint analysis: Median PFS first-line (mo)

<table>
<thead>
<tr>
<th>Everolimus</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.9 (8.3 NGS)</td>
<td>10.7 (10.8 NGS)</td>
</tr>
</tbody>
</table>

Hazard Ratio = 1.4
2-Sided 95% CI [1.2–1.8]
RECORD-3 vs. Published Datasets (Stage I-IV)

PFS1L and PBRM1 Mutation in ccRCC

PBRM1 Mutations: Comparable Benefit from Everolimus and Sunitinib

RED: Everolimus
Blue: Sunitinib

Biomarker and Treatment Group:
- PBRM1 MT (Everolimus)
- PBRM1 MT (Sunitinib)
- PBRM1 WT (Everolimus)
- PBRM1 WT (Sunitinib)
PFS1L and BAP1 Mutation in ccRCC

BAP1 Mutations: Worse on either Everolimus or Sunitinib
Three Distinct ccRCC Molecular Subgroups
Differential Overall Survival on Targeted Therapies
(Treatment Sequence Matters)
<table>
<thead>
<tr>
<th>mTORC1 inhibitor response</th>
<th>Initiating</th>
<th>Early</th>
<th>Intermediate</th>
<th>Late</th>
<th>Speedy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Yes</td>
<td>VHL</td>
<td>MTOR/TSC1/TSC2</td>
<td>MTOR/TSC1/TSC2/ Others?</td>
<td>Others</td>
<td>MTOR/TSC1/TSC2</td>
</tr>
<tr>
<td>2. Yes</td>
<td>VHL</td>
<td>PBRM1</td>
<td>MTOR/TSC1/TSC2/ Others?</td>
<td>Others</td>
<td>MTOR/TSC1/TSC2</td>
</tr>
<tr>
<td>3. ?</td>
<td>VHL</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
<td>MTOR/TSC1/TSC2</td>
</tr>
</tbody>
</table>
PFS1L and KDM5C Mutation in ccRCC
KDM5C Mutations with Exceptional Sunitinib Benefit
KDM5C MT Male Patients are Long-term Responders to Sunitinib

RED: Sun-Eve
Green: Eve-Sun

MT
WT
Proposed 2016 ccRCC Molecular Subgroups
For Precision Therapeutics

Hsieh et al. 2016
25yo Saudi Arabia Male Metastatic Kidney Cancer

Ipi+Nivo plus XRT in 2015

Currently Off Treatment Since Jan 2016
Kidney Cancer Evolution & Therapeutic Opportunities
A Braided River Model

Wei & Hsieh, NRU 2015
Special Thanks to Our Patients & Their Families

Funding
NIH NCI
The Randy & Kathy MacDonald Fund
The Tuttle Fund
The Dahan TFE3 Fund
The Weiss Fund
The Bryan Fund
Rock Out For the Cure
Cycle for Survival
Functional Genomics Initiative
Pfizer Inc.
Novartis Inc.
CGI Inc.
Thank You