Pathway-Directed Treatment Strategies in Kidney Cancer

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Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute
Human Renal Epithelial Neoplasms

- Clear Cell
  - \( VHL \)

- Papillary Type 1
  - \( Met \)

- Chromophobe

- Hybrid
  - \( FLCN \)

- Papillary Type 2
  - \( FH \)

- TFE3
  - \( TFE3, TFEB, MITF \)

- Angiomyolipoma
  - \( TSC1, TSC2 \)

- Oncocytic
  - \( SDHB, SDHC, SDHD \)

- Clear/Chromophobe
  - \( PTEN \)
Renal Cell Carcinoma (RCC)
> 65,000 US/yr
~14,000 deaths US/yr

Clear Cell RCC
~75%-80%

Papillary RCC
~15%

Chromophobe RCC
<5%

Others
<5%

Type 1

Type 2
(Non Type 1)
Clear Cell RCC

- Most common RCC subtype
- Biology and molecular mechanisms better understood than other RCC subtypes
- Characterized by loss of function of \textit{VHL} gene (90%)
- Majority of patients enrolled on contemporary RCC trials have clear cell RCC
Clear Cell Renal Carcinoma
von Hippel Lindau (VHL)

Sporadic

Inherited
VHL Clinical Features

- Tumors develop in:
  - Both Kidneys
  - Adrenal Glands
  - Pancreas
  - Brain or Spine
  - Eyes
  - Inner Ears
von Hippel-Lindau (VHL): Multiple Clear Cell Renal Carcinomas

Multiple Renal Cysts Containing RCC

Clear Cell RCC

J Urol 153:1995
Germline VHL Mutations
Sporadic Clear Cell RCC
Somatic VHL Gene Mutations
HIFα is targeted for degradation in normoxic, but not hypoxic cells.

**Normoxia**

- VHL
- β-domain
- α-domain
- HIF-α
- Degradation

**Hypoxia**

- VHL
- β-domain
- α-domain
- HIF-α
- Accumulation
- VEGF
- Glut 1
- PDGF
Targeting the VHL Pathway in Sporadic Clear Cell RCC

VHL Protein

- \( \beta \) domain

HIF

- mTOR

- VHL Complex Disrupted

Bevacizumab (Antibody)

- VEGF
  - VEGFR
    - Axitinib
    - Pazopanib

- PDGF
  - PDGFR
    - Sunitinib
    - Sorafenib

- HGF
  - MET
    - Cabozantinib

Tensirolimus

PDGF

- PDGFR

VHL Associated Tumors: Principles of Management

• Local Control: Surgery/Ablation
  – Minimize the risk of metastases (RCC, PNET, pheochromocytoma)
  – Control of local symptoms (CNS, retinal, ELST) or systemic complications (pheochromocytoma)

• Metastatic Disease: Systemic Therapy
  – No dedicated/VHL-specific studies
  – Management derived from standard of care for sporadic tumors
Why Should We Explore Alternative Treatment Strategies?

• Current therapy associated with significant morbidity
  
  – Multiple surgeries during a patient’s lifetime
  – Perioperative complications from surgery
  – Gradual loss of renal function, pancreatic or adrenal insufficiency
  – Neurologic deficits

• Lifelong risk of developing new lesions
Systemic Therapy: Alternative to Surgery?

• Goals of Therapy

  – Delay or avoid surgery
    • Prevent tumor growth or reduce tumor size
    • Prevent new tumors
  – Prevent distant spread/metastasis
  – Improve quality of life
  – Preserve function
  – Acceptable short and long term side effects
Systemic Therapy in VHL

- Inhibitors of angiogenesis/VEGFR
  - Sunitinib (Jonasch, MD Anderson)
  - Pazopanib (Jonasch, MD Anderson)
  - Vandetanib (Srinivasan, NCI)

- Targeting HIF
  - 17 AAG (Srinivasan, NCI)
  - PT2385 (Srinivasan, NCI)
  - PT2977 (Multicenter, Peloton Therapeutics)
Targeting VHL/HIF in Clear Cell RCC: Phase 2 Study of Vandetanib
Vandetanib in VHL

Study Design

• Single arm, open label phase 2 study

• Diagnosis of VHL and a measurable renal tumor

• Primary Endpoint
  – RECIST Response rate in renal tumors

• Assess response by RECIST q 12 weeks
Best Response in 37 Patients with VHL-RCC Treated with Vandetanib
37 year old with VHL

Baseline

On Vandetanib
### High Rate of Discontinuation Due to Side Effects

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th># of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt/PI Choice</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Grade 3-4 Toxicity</td>
<td>13 (35%)</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>13 (35%)</td>
</tr>
</tbody>
</table>
Phase 2 Study of Pazopanib in VHL

- 31 patients with renal, CNS or pancreatic tumors

- Pazopanib given for 12 weeks (could be extended if clinical benefit)

- 13 pts (42%) demonstrated a response

- Toxicity/ Intolerability a major issue
  - 18/31 (58%) patients discontinued
    - 1 patient died from a CNS hemorrhage
    - 7 pts discontinued due to severe toxicity (including 4 due to elevated transaminases)
    - 11 patients withdrew (patient choice)

Jonasch et al, ASCO, 2017
# VEGFR TKI: Summary

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pazopanib</th>
<th>Vandetanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>PNET</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>CNS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pheo, ELST</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

## Tolerability

| Discontinued for AE | 57%      | 62%       |
# VEGFR TKI: Summary

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<tr>
<th>Activity</th>
<th>Pazopanib</th>
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</tr>
<tr>
<td>CNS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pheo, ELST</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

## Tolerability

| Discontinued for AE | Pazopanib (57%) | Vandetanib (62%) |
Systemic Therapy for VHL

- Evaluated in small phase 2 studies in localized RCC
  - 17 AAG, Vandetanib, Sunitinib, Pazopanib

- Modest activity

- Side effects of VEGFR-targeted therapy unacceptable to this population

- Not considered standard in pts with organ confined disease; management remains largely surgical
Targeting the VHL Pathway

VHL Protein

\[ \beta \text{ domain} \]

HIF

HIF 2 Inhibitors

- VEGF
  - VEGFR
- PDGF
  - PDGFR
- HGF
  - MET

VHL Complex Disrupted
Development of Small Molecule HIF2α Inhibitor

UT Southwestern (UTSW) research on HIF-2α biology
- Identified small molecule binding pocket in PAS-B domain
- Established that small molecule binding led to inhibition of transcriptional activity

Scheuermann et al. PNAS 2009, 106:450
Key et al. JACS 2009, 131:17647

Slide courtesy of Naseem Zojwalla, Peloton
Development of Small Molecule HIF2α Inhibitor

HIF-2α antagonist bound to HIF-2α PAS-B* domain

HIF-2α PAS-B* (R247E mutant) domain (green)
HIF-1β PAS-B* (E362R mutant) domain (blue)
PT2385 (magenta)

Chen et al. Nature 2016, 539:112
Courtney et al. J Clin Oncol 2018

Slide courtesy of Naseem Zojwalla, Peloton
Development of Small Molecule HIF2α Inhibitor

HIF-2α antagonist bound to HIF-2α PAS-B* domain

PT2385

Chen et al. Nature 2016, 539:112
Courtney et al. J Clin Oncol 2018
PT2385-202 Trial

Phase 2 study of PT2385 in patients with VHL disease-associated RCC

• National Cancer Institute
• Key entry criteria
  – Germline VHL alteration
  – Measurable tumor in kidney
  – Treatment-naïve
  – No metastatic disease
• 4 patients enrolled:
  – Two patients with highest PT2385 drug exposure had tumor shrinkage in renal lesions with one of the patients also having retinal disease that improved on treatment
PT2385-202 Trial

Retinal Lesion Improvement in Patient 001

![Retinal Images]

Baseline (4/27/17)

3 Months (8/2/17)

Baseline (4/27/17)

8 Weeks after PT2385 stop (1/17/18)
HIF2α Inhibitor- PT2385: 1st Generation HIF-2α Inhibitor

• N = 26 in dose escalation at doses of 100-1800 mg PO BID
• N = 25 in expansion at 800 mg PO BID

• Median prior therapies: 4

• Anemia most common adverse event

• ORR: CR 2%; PR 12%; SD 52%

• Higher exposure is associated with antitumor activity
• High variability in drug exposure among patients
Sustained HIF-2α target engagement is necessary to achieve clinically meaningful benefit.

Progression Free Survival for patients experiencing steady-state exposure ≥ 0.5 µg/mL vs. < 0.5 µg/mL trough concentrations (all evaluable patients, n=48)

How to shift patients into the improved PFS group?

Improved exposure

Slide courtesy of Naseem Zojwalla, Peloton
PT2977: A Superior HIF-2α Inhibitor

- PT2977 surmounts the PK limitations of PT2385 and has a comparable safety/tolerability profile
- PT2977 is ~10 times more potent than PT2385
- The recommended Phase 2 dose of PT2977 is 120 mg p.o, q.d.

786-O subcutaneous xenograft model of RCC
A First-in-Human Phase 1/2 Trial of the Oral HIF-2α Inhibitor PT2977 in Patients with Advanced RCC

Toni K. Choueiri¹, Elizabeth R. Plimack², Todd M. Bauer³, Jaime R. Merchan⁴, Kyriakos P. Papadopoulos⁵, David F. McDermott⁶, M. Dror Michaelson⁷, Leonard J. Appleman⁸, Naseem J. Zojwalla⁹, and Eric Jonasch¹⁰

¹Dana-Farber Cancer Institute, Boston, MA; ²Fox Chase Cancer Center, Philadelphia, PA; ³Sarah Cannon Research Institute/Tennessee Oncology, PLLC., Nashville, TN; ⁴University of Miami, Miami, FL; ⁵South Texas Accelerated Research Therapeutics (START), San Antonio, TX; ⁶Beth Israel Deaconess Medical Center, Boston, MA; ⁷Massachusetts General Hospital, Boston, MA; ⁸University of Pittsburgh Medical Center, Pittsburgh, PA; ⁹Peloton Therapeutics Inc., Dallas, TX; ¹⁰MD Anderson Cancer Center, Houston, TX, USA.
HIF2α Inhibitor- PT2977- Best Change in Tumor Size

64% of patients experienced any tumor shrinkage

Best Change in Sum of Target Lesions from Baseline (%)

As of January 01, 2019

* = Continuing on PT2977

Slide courtesy of Naseem Zojwalla, Peloton
HIF2α- PT2977- Duration of Treatment

Best Response | N=55
---|---
PR | 12 (22%)
SD | 31 (56%)
DCR | 43 (78%)

Median Follow up 9 months, 20pts still ongoing as Jan, 2019

As of January 1, 2019

Slide courtesy of Naseem Zojwalla, Peloton
HIF2α- PT2977- Safety

- Anemia
  - Most common AE
  - Expected AE due to Regulation of EPO with HIF2α inhibitors
  - Managed well with EPO replacement as clinically indicated (EPO therapy initiated on average 6-8 weeks)

- Hypoxia
  - Average time of onset is after 3-4 weeks of therapy
  - Majority of cases triggered by an acute event

- No cardiovascular toxicities reported with treatment with HIF2α inhibitors (no Hypertension, no CHF...)

Safety profile compares well with current VEGFR TKI
**PT2977-202 VHL Trial**

*Study Design/Schema*

- **Target Enrollment:** 50 patients treated at 120mg/day
- **Primary Endpoint:** ORR in RCC lesions
  - Radiographic responses must be confirmed at least 4 weeks later
- **Secondary Endpoints:**
  - PFS, DOR, TTR, efficacy in non-RCC lesions, OS, Safety, PK
- **Key Entry Criteria:**
  - Germline VHL alteration
  - At least one measurable solid RCC lesion and no tumors requiring immediate surgical intervention
  - No prior systemic anti-cancer therapy
  - No metastatic disease

---

**Tumor Evaluations**

- PK/PD Pre, 2°, 5°
- PK/PD Pre, 2°, 5°
- First Tumor Evaluation is after 12 weeks of dosing, then Q 12 weeks thereafter

**Screening**

<table>
<thead>
<tr>
<th>Week</th>
<th>PT2977 continuous daily dosing until progression or toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

**Visits every 2-4 weeks for 25 weeks, then every 12 weeks**

**Discontinuation**

- 28 Day follow up visit from last dose of study drug
- Long Term follow up – contact every 6 months for up to 3 years
Study Open at 11 Centers (8 US Centers and 3 European Centers)

- F. Donskov (Aarhus Univ., Denmark)
- T. Else (Univ of Michigan)
- O. Iliopoulos (MGH)
- E. Jonasch (MDACC)
- J. Maranchie (Univ of Pitt)
- B. Maughn (Huntsman)
- S. Oudard (Georges Pompidou, France)
- V. Narayan (Univ of Penn)
- K. Rathmell (Vanderbilt)
- R. Srinivasan (NCI)
- S. Welsh (Univ. of Cambridge, UK)

• ~ March –April, 2019: Accrual Complete

• May, 2019: Peloton Inc acquired by Merck
Therapeutic Strategies in Papillary RCC
Papillary RCC

- Most common nonclear cell variant (10-15% of all RCC)

- Some forms are very aggressive, metastatic disease is uniformly fatal

- No standard options of proven benefit
  - Modest outcomes with VEGF pathway antagonists, mTOR inhibitors and EGFR inhibitors
  - Response rates 0-36%, PFS ~6 months
SYSTEMIC THERAPY

Clinical trial (preferred)
or
Temsirolimus (category 1 for poor-prognosis patients;\textsuperscript{f}category 2A for other risk groups)
or
Sorafenib
or
Sunitinib
or
Pazopanib
or
Axitinib
or
Everolimus
or
Bevacizumab
or
Erlotinib
and
Best supportive care;\textsuperscript{h}

\textbf{See NCCN Guidelines for Palliative Care}

\textsuperscript{f}Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See \textit{Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-B)}.

\textsuperscript{h}Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

\textsuperscript{g}Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine. Partial responses have been observed to cytotoxic chemotherapy (carboplatin + gemcitabine or carboplatin + paclitaxel) with collecting duct or medullary subtypes.
## VEGFR or mTOR Inhibition in Papillary RCC

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>Overall response rate (ORR)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>61</td>
<td>6</td>
<td>&lt;18</td>
<td>12%</td>
<td>Ravaud, Ann Onc</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>27</td>
<td>1.6</td>
<td>12.6</td>
<td>0%</td>
<td>Tannir, Eur Urol</td>
</tr>
<tr>
<td>Everolimus (RAPTOR)</td>
<td>92</td>
<td>3.7</td>
<td>21.1</td>
<td>-</td>
<td>Escudier, ECCO</td>
</tr>
<tr>
<td>Everolimus</td>
<td>49</td>
<td>5.2</td>
<td>-</td>
<td>10%</td>
<td>Koh, Ann Onc</td>
</tr>
<tr>
<td>Everolimus vs Sunitinib (ESPN)</td>
<td>68</td>
<td>4.1</td>
<td>NR</td>
<td>0%</td>
<td>Tannir, ASCO 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs 6.1</td>
<td>vs 10.5</td>
<td>vs vs 12%</td>
<td></td>
</tr>
<tr>
<td>Everolimus vs Sunitinib (ASPEN)</td>
<td>108</td>
<td>5.6</td>
<td>13</td>
<td>9%</td>
<td>Armstrong, ASCO 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs 8.3</td>
<td>vs 32</td>
<td>vs vs 18%</td>
<td></td>
</tr>
</tbody>
</table>
Papillary RCC: Histologic Subtypes

Type 1

Type 2 (Non Type 1)
TCGA Profiling of Papillary RCC: 4 Distinct Subgroups
Targeting the Met Pathway in Papillary RCC
Hereditary Papillary Renal Cancer (HPRC)

- Familial form of type I papillary RCC
- Affected individuals present with bilateral multifocal papillary RCC
MET - The Gene for Hereditary Papillary Renal Cancer

Germline mutations in *MET* are the hallmark of HPRC

Location of *MET* on chromosome 7

Nonrandom duplication of chromosome bearing mutated *MET* allele

Schmidt et al., Nat Genetics, 1997
Understanding the Role of Met in Sporadic Papillary Renal Cancer

- **Activating Mutations in MET**
  - Germline mutations in tyrosine kinase domain (HPRC)
  - Somatic activating mutations seen in ~15% of sporadic papillary RCC
  - \( \text{MET} \) fusion or splice variants ~ 5%

- **Duplication of chromosome 7**
  - ~ 50% - 70% of all papillary RCC
  - Both \( \text{MET} \) and its activating ligand \( \text{HGF} \) located on Ch 7

- **\( \text{MET} \) and Ch7 alterations seen predominantly in type 1 papillary RCC**

Nat Genet 1997; Am J Path 1999; TCGA, NEJM 2015;
Phase II and Biomarker Study of the Dual MET/VEGFR2 Inhibitor Foretinib in Patients With Papillary Renal Cell Carcinoma

Foretinib (XL880)
Kinase Selectivity Profile

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC\textsubscript{50} nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>984</td>
</tr>
<tr>
<td>LTK</td>
<td>1290</td>
</tr>
<tr>
<td>ROS</td>
<td>13</td>
</tr>
<tr>
<td>IGF1R</td>
<td>1710</td>
</tr>
<tr>
<td>IR</td>
<td>102</td>
</tr>
<tr>
<td>INSRR</td>
<td>26</td>
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<tr>
<td>Met</td>
<td>7</td>
</tr>
<tr>
<td>RON</td>
<td>2</td>
</tr>
<tr>
<td>RYK</td>
<td>-</td>
</tr>
<tr>
<td>AXL</td>
<td>2</td>
</tr>
<tr>
<td>Mer</td>
<td>0.6</td>
</tr>
<tr>
<td>Tyro3</td>
<td>0.5</td>
</tr>
<tr>
<td>FGFR1</td>
<td>1006</td>
</tr>
<tr>
<td>FGFR2</td>
<td>832</td>
</tr>
<tr>
<td>FGFR3</td>
<td>1009</td>
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<tr>
<td>FGFR4</td>
<td>2990</td>
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<tr>
<td>RET</td>
<td>0.9</td>
</tr>
<tr>
<td>VEGFR1</td>
<td>5</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>2</td>
</tr>
<tr>
<td>VEGFR3</td>
<td>0.7</td>
</tr>
<tr>
<td>CSF1R</td>
<td>1.7</td>
</tr>
<tr>
<td>Kit</td>
<td>48</td>
</tr>
<tr>
<td>FLT3</td>
<td>1.7</td>
</tr>
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<td>PDGFRA</td>
<td>2.6</td>
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<tr>
<td>PDGFRB</td>
<td>28</td>
</tr>
<tr>
<td>PTK7</td>
<td>-</td>
</tr>
<tr>
<td>ROR1</td>
<td>-</td>
</tr>
<tr>
<td>ROR2</td>
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</tr>
<tr>
<td>DDR1</td>
<td>5.5</td>
</tr>
<tr>
<td>DDR2</td>
<td>0.1</td>
</tr>
<tr>
<td>NTRK2</td>
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<tr>
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<tr>
<td>NTRK1</td>
<td>2.3</td>
</tr>
<tr>
<td>MUSK</td>
<td>NC</td>
</tr>
</tbody>
</table>
Patient Eligibility

- Histologically confirmed locally advanced, bilateral multifocal, or metastatic sporadic papillary RCC

- Central pathology review performed by a single pathologist (Maria Merino, NCI)

- 1 prior systemic therapy allowed
Study Objectives

• **Primary objective:**
  – Overall Response Rate (ORR) by RECIST.

• **Secondary Objectives:**
  - Correlation of MET status (Mutation, Amplification or Trisomy 7) with outcome
  - Progression-Free Survival (PFS)
  - Overall Survival (OS)
  - Safety and tolerability
  - PK parameters and PD markers (plasma HGF, sMET, sVEGFR2 and VEGF) and correlation with outcome (with Don Bottaro)
Primary Endpoint: Overall Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Dosing Cohort A (n=37)</th>
<th>Dosing Cohort B (n=37)</th>
<th>TOTAL (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>5 (13.5%)</td>
<td>5 (13.5%)</td>
<td>10 (13.5%)</td>
</tr>
</tbody>
</table>

- Duration of response: 18.5 months
- Median PFS: 9.3 months
Germline *MET* Mutations Associated with High Response Rate

\[ N = 67 \text{ evaluable:} \]

- Germline *MET* mutation (N=10)
  - Mutated *MET*:
    - 5/10 PR (50%)
    - 5 SD (4 with >10% reduction in SLD of tumors)
  - WT MET:
    - 5/57 (9%)

- Other *MET* alterations
  - *MET* amplification (N=2): No responses
  - Gain chromosome 7 (N=18): ORR 5%
Hereditary Papillary Renal Carcinoma (HPRC) Type 1
Regression of a renal tumor in a patient with HPRC treated with Foretinib

Pre-Treatment

Srinivasan, et al ASCO 2009
Regression of a Renal Tumor in a Patient with HPRC Treated with Foretinib

Pre-Treatment

Following 49 cycles of therapy

Srinivasan, et al ASCO 2009
Targeted Lesions in Patients with Germline $MET$ Mutations
## Treatment-Related Toxicities (≥10%)

<table>
<thead>
<tr>
<th></th>
<th>Intermittent Arm</th>
<th>Daily Dosing Arm</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Grade</td>
<td>Grade 3/4</td>
<td>All-Grade</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (73%)</td>
<td>13 (35%)</td>
<td>33 (89%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 (76%)</td>
<td>2 (5%)</td>
<td>26 (70%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (46%)</td>
<td>5 (13.5%)</td>
<td>24 (65%)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (65%)</td>
<td>0</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (46%)</td>
<td>1 (3%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 (38%)</td>
<td>0</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (24%)</td>
<td>1 (3%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>7 (19%)</td>
<td>0</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (21%)</td>
<td>0</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>Night blindness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (11%)</td>
<td>1 (3%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (11%)</td>
<td>4 (11%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (24%)</td>
<td>1 (3%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (8%)</td>
<td>0</td>
<td>5 (13.5%)</td>
</tr>
</tbody>
</table>
Met Inhibitors in Papillary RCC: Summary

• MET activation status

  – Tumors with germline \textit{MET} mutations sensitive, \textit{BUT}

  – Signs of efficacy in the absence of \textit{MET} mutations (\textit{? VEGFR inhibition})
Met Inhibition in Papillary RCC: Future Plans

- Was optimal Met inhibition achieved?
  - Foretinib dosing limited by toxicity related to VEGFR inhibition
  - Extent of tumor Met inhibition- data not available
  - Are tumors with other forms of MET alterations (duplication of chromosome 7) sensitive, but require higher levels of inhibition?
Selective Met Inhibitor in Papillary RCC

14-C-0037: A Phase 2 Study of the MET Kinase Inhibitor INC280 in Papillary Renal Cell Cancer (NCT02019693)

• Primary endpoint:
  - Overall Response Rate

• Secondary endpoints:
  - Impact of MET status on outcome
  - PFS, OS
  - Modulation of Met activity (phospho-Met) in tumor tissue (with Don Bottaro)
Looking Beyond MET in Type 1 Papillary RCC

• High Incidence of Primary Resistance
  – Low response rates (7-15%) in multiple studies (foretinib, INC280, savolitinib)
  – Role of Met as a driver unclear in the absence of activating mutations
  – Additional genetic alterations

• Secondary Resistance
  – Acquisition of a second MET mutation
  – ?other alterations
### MET Status in Patient-Derived Type1 Papillary RCC Cell Lines

<table>
<thead>
<tr>
<th>Cell line designation</th>
<th>Patient Gender</th>
<th>Age at Surgery</th>
<th>Procurement Source</th>
<th>Primary Tumor Histopathology</th>
<th>Met Mutation</th>
<th>Met Copy number</th>
<th>Other mutations Oncovar V4 analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOK345</td>
<td>male</td>
<td>56</td>
<td>pleural fluid</td>
<td>Type1PRCC</td>
<td>H1112R (germline)</td>
<td>3</td>
<td>CUL3(p.Y753)</td>
</tr>
<tr>
<td>UOK337</td>
<td>male</td>
<td>61</td>
<td>abdominal fluid</td>
<td>Type1PRCC</td>
<td>H1106Q (somatic)</td>
<td>~4</td>
<td>-</td>
</tr>
<tr>
<td>UOK342</td>
<td>male</td>
<td>63</td>
<td>ascites</td>
<td>Type1PRCC</td>
<td>-</td>
<td>7-8</td>
<td>NF2(splice site) KRAS (p.G12C)</td>
</tr>
<tr>
<td>UOK332</td>
<td>male</td>
<td>45</td>
<td>peritoneal fluid</td>
<td>Type1PRCC</td>
<td>-</td>
<td>~4</td>
<td>BAP1 (pH94R)</td>
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</tbody>
</table>
Targeting Metabolic Alterations: Phase 2 Study of Bevacizumab and Erlotinib
Hereditary Leiomyomatosis Renal Cell Carcinoma: HLRCC

- Cutaneous leiomyomas
- Uterine leiomyomas (fibroids)
- Renal cell carcinoma (Type 2 papillary RCC)
HLRCC Associated Kidney Cancer: Principles of Management

- Clinically aggressive phenotype

- Localized disease
  - Rapid growth kinetics
  - Propensity to metastasize early
  - Surgical resection recommended even with small primary

- Metastatic disease
  - Rapidly progressive and uniformly fatal
  - Not sensitive to chemotherapy, IL-2
  - Modest responses to VEGF-targeted therapy
**Fumarate Hydratase:**
HLRCC Kidney Cancer

![Diagram of Fumarate Hydratase and Krebs Cycle](image-url)

- Glucose
- Glycolysis
- Pyruvate
- Acetyl-CoA
- Oxaloacetate
- Citrate
- Malate
- Fumarate Hydratase (FH)
- Fumarate
- α-ketoglutarate
- Succinate
- Succinyl-CoA

Isaacs, Cancer Cell, 2005
Tong, Cancer Cell, 2011
Fumarate Hydratase: HLRCC Kidney Cancer

Glucose → Pyruvate → Acetyl-CoA → Oxaloacetate → Citrate
Malate → Isocitrate → α-ketoglutarate → Succinyl-CoA → Succinate
Fumarate

Krebs Cycle

Cancer Cell, 2005
Cancer Cell, 2011
UOK262: Glucose Dependence in an HLRCC-Derived Cell Line
A Sweet New Role for EGFR in Cancer

Jeffrey A. Engelman¹ and Lewis C. Cantley²,*

¹Massachusetts General Hospital Cancer Center, Boston, MA 02129, USA
²Beth Israel Deaconess Medical Center Cancer Center, Boston, MA 02115, USA
*Correspondence: lewis_cantley@hms.harvard.edu
DOI 10.1016/j.ccr.2006.04.008
Study Design

Metastatic papillary RCC

N=41

Cohort 1 (HLRCC)
N = 20

Bevacizumab 10mg/kg IV q2 weeks
plus
Erlotinib 150 mg PO daily

Cohort 2 (Sporadic)
N = 21
Study Eligibility

- Histologic confirmation of papillary RCC and at least 1 site of measurable disease
- Adequate organ function
- Up to 2 prior VEGF-pathway inhibitors; no prior bevacizumab
- ECOG performance status 0-2
## Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 [HLRCC]</th>
<th>Cohort 2 [Sporadic]</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>20</td>
<td>21</td>
<td>41</td>
</tr>
<tr>
<td>Median Age (range), years</td>
<td>46 (22 – 63)</td>
<td>55 (35 – 73)</td>
<td>52 (22 – 73)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (55%)</td>
<td>15 (71%)</td>
<td>26 (63%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (45%)</td>
<td>6 (29%)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td>MSKCC Risk Groups</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Favorable</td>
<td>5</td>
<td>1</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>12</td>
<td>17</td>
<td>29 (70%)</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>3</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Prior Systemic Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>9</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>12</td>
<td>18 (44%)</td>
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</tr>
</tbody>
</table>
# Bevacizumab plus Erlotinib in Papillary RCC - Efficacy

<table>
<thead>
<tr>
<th>Best Response by RECIST</th>
<th>Cohort 1 [HLRCC] (%)</th>
<th>Cohort 2 [Sporadic] (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=20</td>
<td>N=21</td>
<td></td>
</tr>
<tr>
<td>Confirmed Partial Response (PR)</td>
<td>13 (65%)</td>
<td>6 (29%)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>65%</td>
<td>29%</td>
<td>46%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>7 (35%)</td>
<td>13 (62%)</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Disease Control Rate (SD+PR)</td>
<td>100%</td>
<td>91%</td>
<td>95%</td>
</tr>
</tbody>
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## Bevacizumab plus Erlotinib in Papillary RCC - Efficacy

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<tr>
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<td>100%</td>
<td>91%</td>
<td>95%</td>
</tr>
</tbody>
</table>
K-M Estimate of PFS

Median PFS 12.8 [95% CI 7.47 – 26.3]
K-M Estimate of PFS

Entire study: 12.8 [95% CI 7.47 – 26.3]
HLRCC: 24.2 months [95% CI 12.8 – NR]
Non-HLRCC: 7.4 months [95% CI 3.73 – 10.2]
Bevacizumab plus Erlotinib: Extent of Response
Bevacizumab plus Erlotinib: Response Duration

- Currently on therapy
- HLRCC
- Non-HLRCC

No. of cycles on therapy

Pts with Partial Response

0 10 20 30 40 50

Bevacizumab plus Erlotinib: Response Duration

- Currently on therapy
- HLRCC
- Non-HLRCC

No. of cycles on therapy

Pts with Partial Response

0 10 20 30 40 50
58 Year Old Man with HLRCC Associated Papillary RCC

Baseline PET/CT
58 Year Old Man with HLRCC Associated Papillary RCC

Baseline PET/CT

Following 4 Months of Therapy
58 Year Old Man with HLRCC Associated Papillary RCC
58 Year Old Man with HLRCC Associated Papillary RCC

Before Treatment

Following 4 Months of Therapy
36 Year Old Woman with HLRCC Associated Papillary RCC
Bevacizumab *plus* Erlotinib

HLRCC Associated Kidney Cancer

- Promising activity in HLRCC

- Study expanded to include an additional cohort of HLRCC patients
Bevacizumab plus Erlotinib

Sporadic Papillary RCC

• PFS comparable to other strategies in papillary RCC

• Responses following failure of other targeted/ VEGFR pathway agents

• Striking and durable responses in some patients with sporadic papillary RCC
Bevacizumab \textit{plus} Erlotinib: Future Directions

• How can we select sporadic papillary RCC patients likely to respond?

  – Histologic subtype
    • Type 1: 1/8 PR (13%)
    • Type 2: 5/13 PR (39%)

  – Evaluating potential molecular markers
    • Somatic mutations in \textit{FH}
    • EGFR
    • Other/related pathways, e.g, NRF2/Cul3/Keap1
Bevacizumab *plus* Erlotinib: Future Directions

Metastatic papillary RCC

N = 41

Bevacizumab 10mg/kg IV q2 weeks *plus* Erlotinib150 mg PO daily

- Cohort 3 (HLRCC) N = 20
- Cohort 4 (Sporadic) N = 20
- Cohort 3 (HLRCC) N = 20
- Cohort 4 (Sporadic) N = 20
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OP3 Staff
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