Targeting HIF-2 in renal cancer

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COI: Patent HIF-2 biomarker
Research funding – Peloton Therapeutics

Development of a HIF-2 inhibitor (HIF2-I)

High-Throughput Screen

Scheuermann et al. Nat Chem Biol 2013

Scheuermann et al. PNAS 2009

HIF-2α HIF-1β
HRE (DNA)

HIF2-I
PT2399

Validating HIF-2 as a target for ccRCC

>100 lines

Pavia-Jimenez et al., Nat Protoc 2014
Validating HIF-2 as a target

Unsupervised hierarchical clustering of gene expression shows similarities between tumors and corresponding tumorgrafts

HIF2-I (PT2399) is active against human ccRCC transplants in mice

HIF2-I (PT2399) is active in 50% of ccRCC

HIF2-I (PT2399) has greater activity than sunitinib and is better tolerated
HIF2-I (PT2399) inhibits proliferation & angiogenesis in sensitive ccRCC

HIF2-I (PT2399) suppresses VEGF only in the tumor

HIF2-I (PT2399) dissociates HIF-2 in both sensitive & resistant tumors

HIF2-I (PT2399) is a highly specific inhibitor

Chen et al., Nature 2016
Higher HIF-2α in sensitive tumors

Chen et al., Nature 2016

Identification of biomarkers of HIF-2-dependency

Chen et al., Nature 2016

Acquired resistance?

HIF-2α and HIF-1β mutants preserve HIF complexes despite HIF2-I (PT2399)

Chen et al., Nature 2016
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>66 (29-82)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 16 (31%)  Female: 36 (70%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0: 16 (31%)  1: 25 (49%)  2: 3 (6%)  3: 1 (2%)</td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>42 (82%)</td>
</tr>
<tr>
<td>Sites of metastasis</td>
<td>Lung: 22 (89%)  Node: 19 (75%)  Bone: 12 (48%)  Liver: 11 (43%)</td>
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<tr>
<td>Adjuvant</td>
<td>Yes: 11 (22%)  No: 3 (6%)  6 (12%)</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>6 (12%)  8 (16%)  11 (22%)</td>
</tr>
<tr>
<td>Prior antiangiogenic therapy</td>
<td>51 (20%)  31 (61%)  9 (35%)</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor</td>
<td>11 (22%)  10 (20%)</td>
</tr>
<tr>
<td>AML/MDS selected</td>
<td>Flavopiridol (9 patients)  12 (24%)  Intermediate risk (12 patients)  27 (53%)</td>
</tr>
<tr>
<td>High risk (4 patients)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

Pharmacokinetics & Pharmacodynamics

Baseline Characteristics

Baseline Characteristics

Toxicity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1/2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>7 (14%)  2 (4%)  1 (2%)  10 (20%)</td>
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<tr>
<td>Blood creatinine increased</td>
<td>1 (2%)  3 (6%)  3 (6%)  1 (2%)</td>
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<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>1 (2%)  2 (4%)  3 (6%)  6 (12%)</td>
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<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>6 (12%)  6 (12%)  9 (18%)  11 (22%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (4%)  2 (4%)  2 (4%)  6 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (4%)  2 (4%)  2 (4%)  6 (12%)</td>
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</tr>
<tr>
<td>Increased platelet count</td>
<td>6 (12%)  1 (2%)  1 (2%)  8 (16%)</td>
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<tr>
<td>Decreased platelet count</td>
<td>1 (2%)  1 (2%)  1 (2%)  3 (6%)</td>
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<tr>
<td>Dehydration</td>
<td>5 (10%)  5 (10%)  9 (18%)  14 (28%)</td>
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<td></td>
<td></td>
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<tr>
<td>Nausea</td>
<td>5 (10%)  5 (10%)  9 (18%)  14 (28%)</td>
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<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>2 (4%)  2 (4%)  2 (4%)  6 (12%)</td>
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</tbody>
</table>
Duration of Treatment

Prolonged stable disease in heavily pretreated patient (7 prior lines)

Higher exposure correlates with anti-tumor activity

A First-in-Human Phase 1 Dose-Escalation Trial of the Oral HIF-2α Inhibitor PT2977 in Patients with Advanced Solid Tumors

Presented By Kyriakos Papadopoulos at 2018 ASCO Annual Meeting
Second generation inhibitor, PT2977 – greater potency in preclinical models

- In vivo, PT2977 is ~10x more potent than PT2385

PT2977 Phase I

All-Cause Adverse Events ≥ 10%

- No treatment related DLT at any dose level
- Anemia well managed with EPO replacement

PT2977 Phase I Pharmacokinetics

- Exposure increases with dose up to 120 mg
- Minimal increase in exposure from 120 to 160 mg

PT2977 - Pharmacodynamics

- PT2977 treatment leads to rapid and dose-dependent hemoglobin levels demonstrating target engagement

PT2385
Presented By Kyriakos Papadopoulos at 2018 ASCO Annual Meeting

**Inclusion Criteria:**
- von Hippel Lindau disease with a germline VHL mut.
- At least 1 measurable solid RCC tumor (diagnosis of RCC can be radiologic).
- VHL disease-associated tumors in other organ systems.

**Exclusion Criteria:**
- Prior systemic anti-cancer therapy (includes anti-VEGF therapy and investigational agents).
- Immediate need for surgical intervention for tumor treatment.
- Metastatic disease.

**Conclusions**
- HIF-2 is a valid target in ccRCC.
- Inhibition of the HIF-2 transcription factor abrogates tumor growth in >50% of human ccRCC tumors implanted in mice, including tumors resistant to sunitinib.
- HIF2-I effectively (and specifically) dissociates HIF-2α from HIF-1β in human ccRCC implanted in mice.
- HIF-2 inhibition results in the downregulation of HIF-2 target genes and decreased circulating levels of tumor-produced VEGF.
- HIF-2 inhibitors are more effective and better tolerated than sunitinib in TG models.
- Primary resistance occurs despite dissociation of the HIF-2 complex in tumors.
- Sensitive and resistant tumors can be distinguished by HIF-2α levels and gene expression.
- Resistance develops in sensitive tumors due to binding site and "second-site suppressor mutations."
- A Phase I clinical trial of PT2385 showed that HIF-2 inhibitors are safe and may benefit a subset of patients, but resistance develops.
- Second generation inhibitors (PT2799) have greater potency.
- HIF-2 inhibitors are well tolerated and associated with anemia. Close monitoring for hypoxia is needed (which can be severe).