VHL Research Update: Clinical Trials

Ramaprasad Srinivasan, M.D., Ph.D.
Investigator and Head, Molecular Cancer Section
Urologic Oncology Branch
Center for Cancer Research
National Cancer Institute

Management of VHL Associated Tumors

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

• Associated with significant lifetime morbidity
  – Complications from surgery
  – Gradual loss of renal function, pancreatic or adrenal insufficiency
  – Neurologic deficits

Systemic Therapy as an 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

HIFα is Upregulated in VHL Tumors

VHL

HIF-α

Degradation

Normoxia

Hypoxia or Loss of VHL

VEGF

Glut 1

PDGF

MET

HIF-α Accumulation
Targeting the VHL Pathway

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)

Evaluation of Pazopanib in VHL

- Single arm phase 2 study (N=31)

- Eligibility
  - Clinical features consistent with VHL
  - Presence of one or more of the following
    - Renal tumor or cyst with a solid component >1cm
    - CNS hemangioblastoma >0.5cm
    - Pancreatic NET or cystadenoma

Jonasch et al, Lancet Oncol, 2018
Pazopanib in VHL

- Starting Dose: Pazopanib 800 mg qd
- Duration of therapy:
  - Initial: 24 weeks
  - Subsequent: Patients had the option of continuing beyond 24 weeks if benefiting
- Response evaluated by organ site and by individual lesion
- Early stopping rule for toxicity

Pazopanib in VHL - Efficacy

- Median follow up: 12 months (IQR 7-32)
- Median Duration of Therapy: 6 cycles (IQR 1-36)
- Organ based response:
  - PR in 13/42 (42%)
- Lesion based response:
  - RCC: 31/59 (52%)
  - Pancreatic: 9/17 (53%)
  - CNS: 2/49 (4%)

Evaluating Toxicity

- Standardized criteria based on severity
  - Grade 1: Mild-No intervention
  - Grade 2: Moderate, minimal impact
  - Grade 3: Severe, limiting, intervention/hospitalization
  - Grade 4: Life threatening
  - Grade 5: Death
- Does not always account for chronicity or how the patient’s quality of life is affected

Pazopanib - Tolerability

- Grade 3-4 AE: 10 events
  - Most common: AST/ALT elevation 4/31 (13%)
- One patient died from CNS bleeding
- Dose Modifications:
  - 10/31 (32%) continued starting dose throughout
  - All others required a dose reduction or discontinued early
Pazopanib-Tolerability

- Reasons for Study Drug Discontinuation
  - Grade 3-4 toxicity: 7/31 patients (22%)
  - Patient choice: 11/31 (35%)
    - Adverse impact on quality of life, logistics
  - Death: 1/31 (3%)
  - Progressive Disease: 6/31 (18%)

Vandetanib in VHL

National Cancer Institute (08-C-0020)

- Vandetanib is a dual tyrosine kinase inhibitor with activity against VEGFR2 and EGFR
- Additional activity against RET (approved in Medullary Thyroid Cancer) and Abl

Vandetanib in VHL

- Single arm phase 2 study
- N=37
- Eligibility
  - Clinical features consistent with VHL
  - Presence of at least one measurable renal tumor (RECIST 1.1)
    - Non renal tumors (PNET, CNS hemangioblastoma, pheochromocytoma) followed but not sufficient/required for study entry
- Starting Dose: Vandetanib 300 mg qd
- Duration of therapy:
  - Until progression or unacceptable toxicity
- Response evaluated by organ site and by individual lesion
Vandetanib in VHL-Efficacy

- Median Duration of Therapy: 5.5 months (IQR 2.7-11.1 months)
- 30 patients had at least one follow up scan
- Overall response
  - PR: 1/37 (3%)
  - Tumor Regression < PR: 13/37 (35%)

Vandetanib - Tolerability

- Grade 3-4 AE: 14/37 pts
  - Most common: QT prolongation, HTN, AST/ALT elevation
- Dose Modifications:
  - 12/37 (32%) required a dose reduction
  - Frequent drug interruptions

Vandetanib-Tolerability

- Reasons for Study Drug Discontinuation
  - Toxicity: 13/37 patients (35%)
  - Patient choice: 10/37 (27%)
    - Adverse impact on quality of life
  - Progressive Disease: 11/37 (30%)
Common Side Effects

- Fatigue
- GI Side Effects
  - Diarrhea
  - Nausea/vomiting
  - Altered taste and appetite
- Hypertension
- Skin and hair changes
- Liver inflammation
- ECG changes, changes in mood/sleep (vandetanib)

VEGFR TKI: Summary

<table>
<thead>
<tr>
<th></th>
<th>Pazopanib</th>
<th>Vandetanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>+++</td>
<td>++</td>
</tr>
<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>
<tr>
<td>Tolerability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued for AE</td>
<td>57%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Other considerations:

- Relatively short duration of treatment
  - ~ 6 months
  - Long term side effects unknown
  - Long term benefits remain to be determined
- Do these treatments prevent the developments of new lesions?
Targeting the VHL Pathway

HIF-2α is the Oncogenic Driver in RCC

Small Molecule Inhibition of HIF-2α
Disruption of HIF-2α/HIF-1β Heterodimerization

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

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.

Clinical Trials in VHL-Summary
- Experience restricted to small single arm phase 2 studies
- VEGFR and HIF primary targets pursued
- Tumor regression with VEGFR inhibitors, but patient tolerability a significant issue: long term clinical benefit unknown
- HIF 2 inhibitors offer a new avenue of investigation
Acknowledgements

• Patients and their families

• VHL Care Providers, Researchers, Support Groups

Marston Linehan, M.D.
Adam Metwalli, M.D.
Geonady Bratslavsky, M.D.

UOB laboratory
Laura Schmidt, Ph.D.
Christopher Ricketts, Ph.D.
Carole Sourbier, Ph.D.
Masaya Saka, M.D., Ph.D.
Hisashi Hasumi, M.D., Ph.D.
Yukiko Hasumi, M.D., Ph.D.
Den Crooks, Ph.D.
Youfeng Yang, M.S.
Ming Wei, M.S.

Len Neckers, Ph.D.
Don Eddarano, Ph.D.
Cathy Vocke, Ph.D.
Robert Worrell, Ph.D.

Neurology:
Kareem Zaghoul, M.D.
Prashant Chittiboina, M.D.

General Surgery
Maybeth Hughes, M.D.
Udal Khamnita, M.D.
Prakash Pandalai, M.D.
Electron Kebebe, M.D.

Ophthalmology:
Emily Chew, M.D.
Henry Wiley, M.D.

Endocrinology:
Karel Pacak, M.D.