Clinical Trials in VHL: Past and Present

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
  – Neurologic complications

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

[Diagram showing the upregulation of HIFα in normoxia and hypoxia or loss of VHL]

Normoxia

Hypoxia or Loss of VHL
Targeting the VHL Pathway

VHL Clinical Trials

- Local Therapy
  - Intraocular therapy

- Systemic Therapy
  - Focused on specific organ systems
  - Focused on multiple organ systems

Intraocular Therapy

- Targeting blood vessel growth/angiogenesis
  - Small studies of agents targeting the VEGF axis
  - Ranibizumab pilot study of 5 patients (Chew, NCI)
  - No change in size of retinal angiomas
  - Some decrease in surrounding edema
  - Not considered worthy of further development

- Combination of the PDGF Antagonist E10030 and the VEGF Antagonist Ranibizumab (Chew, NCI)

Systemic Therapy for Retinal Angiomas

- Pilot study of sunitinib (Emily Chew, NCI)
  - 3 patients
  - No effect on retinal lesions
  - Treatment stopped in 2 due to side effects

- Propranolol (Gonzalez-Rodriguez)
  - 7 patients
  - Well tolerated
  - No change in tumor size; reduced edema
Systemic Therapy for CNS Hemangioblastomas

- **Bevacizumab** (Pipas, Dartmouth-Hitchcock)
  - Study terminated
  - No data available

- **Vorinostat** (Chittiboina, NIH)
  - Administered prior to surgery
  - Study completed
  - No data available

Trials Evaluating Effects of Systemic Therapy on Multiple Organ Systems

- **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 daily 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
- Lesion based response:
  - RCC: 26/66 (39%) demonstrated regression
  - Pancreatic: 0/2 (0%), CNS: 0/2 (0%)
- 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: Proportion of intended doses received- Median 69% (IQR 52-82)

Vandetanib-Tolerability

- Reasons for Study Drug Discontinuation
  - Toxicity: 13/37 patients (35%)
  - Patient choice: 10/37 (35%)
    - 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

- 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?

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>55%</td>
<td>62%</td>
</tr>
</tbody>
</table>

VHL Deficiency and HIF-2α Activation

HIF-2α is the Oncogenic Driver in RCC

- >90% of patients with sporadic ccRCC have defective pVHL
- Loss of VHL results in constitutive activation of HIF-2α
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

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.
• Target Enrollment: 50 patients treated at 120mg/day
• Primary Endpoint: ORR in RCC lesions
  – Radiographic responses must be confirmed at least 4 weeks later
• 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

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

Acknowledgements

Marston Linehan, M.D.
Peter Plzo, M.D.
Adam Metwalli, M.D.
Piyush Agarwal, M.D.

UOB laboratory
Laura Schmidt, Ph.D.
Christopher Ricketta, Ph.D.
Carole Sourbier, Ph.D.
Masaya Baba, M.D., Ph.D.
Hiashi Hasumi, M.D., Ph.D.
Yuki Hasumi, M.D., Ph.D.
Dan Crooks, Ph.D.
Youfeng Yang, M.S.
Ming Wei, M.S.

Len Reckers, Ph.D.
Don Bottaro, M.D.
Cathy Vocke, Ph.D.
Robert Worrell, Ph.D.

Neurosurgery:
Kareem Zaghloul, M.D.
Prashant Chittiboina, M.D.

General Surgery
Marybeth Hughes, M.D.
Udai Kammula, M.D.
Prakash Pandalai, M.D.
Electron Kebebew, M.D.

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

Endocrinology:
Karel Pacak, M.D.