Clinical Trials in VHL: Update

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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 as an Alternative to Surgery

Goals of Therapy

– Delay or avoid surgery
  • Prevent tumor growth/reduce tumor size
  • Prevent new tumors
– Prevent distant spread/metastasis
– Improve quality of life
– Preserve function
– Acceptable short and long term side effects
Identification of the VHL gene
(W. Marston Linehan and Berton Zbar, NCI)
Germline VHL Mutations
HIF-α is upregulated in VHL tumors.

Normoxia

1. Hypoxia or loss of VHL leads to HIF-α accumulation.
2. HIF-α is degraded by the proteasome.
3. Prolyl hydroxylation by factor (proteins).
4. HIF-α is hydroxylated by prolyl hydroxylase domain proteins (PHDs).

VHL

VEGF

Glut 1

PDGF

MET
THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2019

William G. Kaelin Jr. Sir Peter J. Ratcliffe Gregg L. Semenza

“for their discoveries of how cells sense and adapt to oxygen availability”

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET
Targeting the VHL Pathway

- **VHL Protein**
- **β domain**
- **VHL Complex Disrupted**

**HIF**

- **HIF 2 Inhibitors**

**VEGF**
- Bevacizumab (Antibody)
- Axitinib
- Pazopanib

**PDGF**
- Sunitinib
- Sorafenib

**HGF**
- Cabozantinib

**VEGFR**
**PDGFR**
**MET**
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)
## VEGFR TKI: Summary

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**Toxicity**

- Discontinued for toxicity: 57% for Pazopanib, 62% for Vandetanib
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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?
Propranolol

• Beta blocker

• Used to treat a variety of conditions
  – Hypertension
  – Pheochromocytoma
  – Tremors
  – Arrhythmias
  – Migraine
Propranolol Induces Infantile Hemangioma Regression

Leaute-Labrèze et al. NEJM
Propranolol suppresses HIF2 alpha *in vitro*
Propranolol is effective in a mouse xenograft model of VHL-/- tumors

Nude mice with 786-O

A

B

C

D

HIF2alpha
Propranolol Curtails HB Growth in Patients (Retrospective)

- 3 patients who started propranolol
- 66 tumors total amongst 3 patients
- 25 had evidence of growth

- Growth Rate Prop: 13.3mm³/year
- Growth Rate Off: 27.1mm³/year

- P<0.0004
Propranolol for CNS Hemangioblastomas
(P. Chittiboina, NIH)
Eligibility and Study Design

Inclusion criteria

- Patients >18 years-old
- Demonstrated radiographic progression of one or more hemangioblastoma within the past 12 months
- Patient without neurologic symptoms attributed to any hemangioblastoma

Exclusion criteria

- History of a non-VHL cancer (except, VHL related clear cell renal cell carcinoma, non-melanoma skin cancer or carcinoma in-situ of the cervix)
- Unable or unwilling to have an Magnetic Resonance Imaging (MRI) with intravenous gadolinium contrast.

Patient with asymptomatic VHL-associated hemangioblastoma

Screening Eligible for Propranolol Therapy

Propranolol Titration
- 1mg/kg/day or week 1-2
- 2mg/kg/day for week 3-4
- 3mg/kg/day for weeks 5+

Follow up:
- Week 5, week 16, week 30, week 56
Targeting the VHL Pathway

VHL Protein

β 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

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

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PT2385

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

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%

• High variability in drug levels among patients
How to shift patients into the improved PFS group?

Improved exposure

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)

HIF2α Inhibitor- PT2385: 1st Generation HIF-2α Inhibitor

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

Slide courtesy of Naseem Zojwalla, Peloton
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

* = Continuing on PT2977

As of January 01, 2019

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

As of January 1, 2019

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

Median Follow up 9 months, 20pts still ongoing as Jan, 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
• **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)
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  - 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**
Data analysis-?2020

Is there a path to FDA approval if phase 2 data promising?
- Approval based on single arm phase 2 data, albeit infrequently (e.g., sunitinib initially approved based on high response rates, avelumab for Merkel cell carcinoma)
- Often requires a confirmatory study demonstrating clinical benefit (improvement in survival or other clinically meaningful endpoints)

Can VHL patients get this drug now?
- Can only get access through a clinical trial- no trial actively accruing at this time
- Unclear if another trial is forthcoming
- ‘Off label’ use?- May be an option if agent approved for another indication, such as sporadic clear cell RCC
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• Patients and their families

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