Evolution of Systemic Therapy Clinical Trials in VHL

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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

Challenges in Designing Clinical Trials for VHL Disease

- Risk Appraisal:
  - Most patients have localized, slow growing disease
  - Long life expectancy
  - Potential for unique complications
  - Potential for altering the biology
- Evaluating Benefit:
  - Multiple organ systems affected-? Different biology
  - Ascertain meaningful clinical benefit

Surgical History: 52 year old woman

- 1982: Resection of CNS hemangioblastoma
- 1990: Resection of Spine Hemangioblastoma
- 1991: Bilateral Partial Nephrectomy, Partial Pancreatectomy
- 1993: Resection of Brain/Spine Hemangioblastoma
- 1994: Resection of Spine Hemangioblastoma
- 2003: Left Lap RFA
- 2004: Right Percutaneous RFA
- 2008: Lt Open Partial Nephrectomy
- 2009: Resection of CNS hemangioblastoma
- 2011: Total Pancreatectomy
- 2012: Left Open Partial Nephrectomy
- 2012: Rt Open Part Nephrectomy
HIFα is targeted for degradation in normoxic, but not hypoxic cells

**Evaluation of Sunitinib in VHL**
- Pilot study (N=15)
- Patients with renal or pancreatic tumors, CNS hemangioblastomas, or retinal angiomas
- Sunitinib administered at standard doses (50mg/d, 4 weeks on, 2 weeks off) for 6 months

**Sunitinib in VHL-Efficacy**
- 15 patients enrolled
- Response in Individual Lesions
  - Renal tumors- 6/18(33%)
  - Pancreatic tumors- 0/5
  - CNS Hemangioblastomas -0/21

Sunitinib in VHL-Tolerability

• Grade 3 AEs- 5/15 (13%)

• Dose Modification
  – Reduction in dose:10/15 (66%)
  – Permanent Discontinuation: 6/15 (40%)
  • Intolerable side effects: 3/15
  • Grade 3-4 AE: 1/15
  • PD: 2/15

Evaluation of Pazopanib in VHL

• Single arm phase 2 study

• 31 patients treated

• 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

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%)
Pazopanib: Response by Individual Lesion

Renal (N=59)

Pancreatic (N=17)

CNS (N=49)

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

Vandetanib in VHL

- 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%)

Baseline ~2 yrs on therapy
**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%)

**VEGFR TKI: Summary**

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<tr>
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<th>Pazopanib</th>
<th>Vandetanib</th>
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<tr>
<td>Activity</td>
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<tr>
<td>RCC</td>
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<td>PNET</td>
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<tr>
<td>Tolerability</td>
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<td>Discontinued for AE</td>
<td>55%</td>
<td>62%</td>
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**Targeting HIF in Clear Cell RCC**

- VHL Protein
- VHL Complex Disrupted
- HIF
- VEGF
- PDGF
- HGF
- MET
Benzoquinone Ansamycins: The First Identified HSP90 Inhibitors

**Geldanamycin**
- Proposed mechanism: tyrosine kinase inhibition
- Later found to be caused by drug-induced kinase degradation
- Direct binding of this drug to HSP90: its true molecular target (Whitesell et al. *PNAS*, 91:8324, 1994)

The Hsp90 chaperone machine is driven by ATP hydrolysis

**Geldenamycin**
- Blocks HSP90-HIF
- VHL Complex Disrupted-RCC
- HIIF1-α accumulation
- Hsp-90
- VEGF
- Glut-1
- TGF-α, EGFR

17-allylamino-17-demethoxygeldanamycin (17 AAG) in VHL
- Single center study at the NCI (2004)
- Single arm phase 2 study
- Eligibility
  - Clinical diagnosis of VHL
  - One or more measurable renal tumors (RECIST)
  - Adequate organ function
  - ECOG ≤ 2
**17AAG in VHL**

**Design:** Open Label Phase II Study

VHL patient with one or more localized renal tumors for which surgery is recommended

17 AAG (300 mg/m² IV) weekly on Days 1, 8, 15 of each 28 day cycle for 3 cycles (12 weeks)

Re-staging at 12 weeks to assess radiological response

CR or PR and no renal tumor ≥3 cm

Yes

Continue 17 AAG for 3 more cycles

No

Surgical resection as clinically indicated

Surveillance until surgical resection

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**17AAG in VHL - Efficacy**

- Trial discussed with over 100 patients

- 9 patients enrolled (7 evaluable)
  - Mean age 48
  - Avg # of tumors 3.3
  - Avg size 3.1 cm

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**17AAG in VHL - Tolerability**

- No Grade 3/4 events related to drug

- Most common toxicities include
  - Nausea (88%)
  - Fatigue (63%)
  - Cardiac (63%)
    - 1st and 2nd degree AV block
    - Sinus Brady and Sinus Tach
    - Non-sustained V-tach
    - One patient developed asymptomatic high grade AV block
  - Dysgeusia (50%)
  - Elevated glucose (50%)
  - Myalgias (38%)

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**17AAG in VHL**

- All 7 evaluable patients were found to have stable disease following 3 cycles of therapy

- No objective responses by RECIST

- Study halted/trial closed due to slow accrual
• 90% of patients with sporadic ccRCC have defective pVHL
• Loss of VHL results in constitutive activation of HIF-2α

VHL Deficiency and HIF-2α Activation
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

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
- 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

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