Systemic Therapy for VHL

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FDA Approved Targeted Therapy for Metastatic Kidney Cancer

- Sunitinib
- Sorafenib
- Axitinib
- Pazopanib
- Bevacizumab (in combination with interferon)
- Temsirolimus
- Everolimus
von Hippel-Lindau (VHL): Multiple Clear Cell Renal Carcinomas

- Multiple Renal Cysts Containing RCC
- Clear Cell RCC

*J Urol* 153:1995
Is There a Need for Systemic Therapy Options in VHL?

- Standard of care: Surgical resection
- Surgery not curative
- Recommended for RCCs ≥ 3cm to minimize risk of metastatic disease
- Patients undergo multiple surgical procedures during their lifetime
- Increasing risk of surgical complications and morbidity with each successive surgery
Goals of Therapy

• Delay/eliminate surgery
  • Induce tumor regression
  • Stabilize or slow tumor growth

• Symptom management

• Prevent metastatic spread

• Acceptable risks/side effects
Germline VHL Mutations
HIFα is targeted for degradation in normoxic, but not hypoxic cells.
Targeting the VHL Pathway in Clear Cell RCC

Adapted From Linehan et al., Ann Rev Med (61); 2010
Targeting VHL/HIF

VHL → HIF

- HSP90 Inhibitors (17 AAG)
  - VEGF → VEGFR
  - PDGF → PDGFR
  - TGF-α → EGFR
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)
Geldenamycin blocks HSP90-HIF

VHL Protein

- $\beta$-domain
- Mutant $\alpha$-domain

VHL Complex Disrupted-RCC

$\text{CUL2}$

$\text{E2}$

$\text{Elongin B}$

$\text{Elongin C}$

Geldanamycin (17AAG)

HIF1-$\alpha$

Accumulation

Hsp-90

VEGF

Glut-1

TGF-$\alpha$, EGFR

Isaacs, et al JBC: 277, 2002
04-C-0238: A Phase 2 Study of 17-allylamino-17-demethoxygeldanamycin (17AAG) in Patients with von Hippel Lindau (VHL) Disease and Renal Tumors
17AAG in VHL

• Study Objectives
  – Primary: Evaluate efficacy (overall response rate) of single agent 17 AAG on renal tumors in patients with VHL disease
  
  – Secondary-Safety and tolerability in VHL patients, Effect on non-renal VHL tumors, HSP90 modulation in PBMC and tumor tissue, feasibility of PET and DCE-MRI in evaluating VHL renal tumors
**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

↓

Surveillance until surgical resection

**No**

Surgical resection as clinically indicated
Results and Conclusions

• 9 patients enrolled (7 evaluable)
  – Mean age 48
  – Avg # of tumors 3.3
  – Avg size 3.1 cm
17AAG in VHL

• Safety:
  – 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%)
17AAG in VHL

- All 8 evaluable patients were found to have stable disease following 3 cycles of therapy

- No objective responses by RECIST

- Trial closed due to slow accrual
17AAG in VHL- Summary

• Acceptable safety profile

• Efficacy-No objective responses, but drug may be cytostatic

• Newer generation HSP90 analogues now available and may bear further investigation as single agents or in combination
# Sunitinib vs IFN-α in Sporadic Clear Cell RCC: Results

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib N=375</th>
<th>IFN N=375</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective RR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>44%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>40%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>11 months</td>
<td>5 months</td>
</tr>
</tbody>
</table>

Motzer, et al JCO 2009
Sunitinib in VHL
(E Jonasch et al., Annals of Oncology, 2011)

• Phase II study (N=15)

• Patients with renal or pancreatic tumors, CNS hemangioblastomas, or retinal angiomas

• Sunitinib administered at standard doses for 4 cycles (6 months)
Sunitinib in VHL: Efficacy

- 15 patients enrolled

- Response measured in individual tumors:
  - 6/18 renal tumors
  - 0/5 pancreatic tumors
  - 0/21 hemangioblastomas
  - 0/7 retinal angiomas
Sunitinib in VHL: Tolerability

- Severe toxicity (grade 4) not seen
- Fatigue and hand foot syndrome most common grade 3 AEs

**BUT**

- Only 9/15 patients able to complete all 4 cycles
  - 3 patients withdrew - Quality of life issues
  - 1 patient discontinued for toxicity
08-C-0020: Phase II Study of ZD6474 (vandetanib) in Patients with von Hippel Lindau (VHL) Disease and Renal Tumors
Targeting VHL/HIF in Clear Cell RCC

- VHL
- HIF
  - VEGF
    - VEGFR
  - PDGF
    - PDGFR
  - TGF-α
    - EGFR

ZD6474
Vandetanib in VHL

- Vandetanib is a dual tyrosine kinase inhibitor with activity against:
  - VEGF2 (mediates tumor angiogenesis)
  - EGFR (mediates tumor growth and proliferation)
Vandetanib in VHL

Objectives

• Primary
  – Overall response rate in VHL patients with renal tumors

• Secondary
  – Safety and tolerability in VHL patients
  – Progression-free survival
  – Effect of ZD6474 on VHL non-renal tumors
  – PD endpoints
Vandetanib in VHL

Study Design

• Single arm, open label phase 2 study
• ZD6474 oral
  – Continuous daily dosing-300mg/day
• Simon optimal two stage design
  – Initial stage: 12 patients
  – If 1 or more of initial 12 respond, maximum of 37 patients will be enrolled
• Assess response by RECIST q 12 weeks
Vandetanib in VHL

Key Eligibility Criteria

• Clinical diagnosis of VHL

• One or more measurable renal tumors

• Adequate organ function

• ECOG ≤ 2
### Vandetanib in VHL: Patient Demographics

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>37</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>47 (28-72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (57%)</td>
</tr>
<tr>
<td>Previous renal procedures (median, range)</td>
<td>3 (0-8)</td>
</tr>
<tr>
<td># of target lesions (median, range)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Tumor diameter (cm) (mean, range)</td>
<td>2.3 (1.2-4.0)</td>
</tr>
</tbody>
</table>
Vandetanib in VHL: Efficacy

Change in Sum of Longest Dimension
Vandetanib in VHL: Efficacy

Table 2: Overall Tumor Best Response

<table>
<thead>
<tr>
<th>RECIST Response</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>26 (77%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>0</td>
</tr>
</tbody>
</table>
# Vandetanib in VHL: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. with &gt; Grade 2 or (%)</th>
<th>No. with &gt; Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash/dermatologic abnormality</td>
<td>24 (19.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Prolonged QTc interval</td>
<td>14 (11.5%)</td>
<td>4 (40.0%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9 (7.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Mood disturbance (anxiety/depression)</td>
<td>9 (7.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8 (6.6%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>7 (5.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (5.7%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>Elevated ALT/AST</td>
<td>6 (4.9%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (3.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2 (1.6%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>Elevated CPK</td>
<td>2 (1.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>2 (1.6%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>122</strong></td>
<td>10</td>
</tr>
</tbody>
</table>

* Only those events with > 1% incidence are listed

^ Total includes all adverse events, including those with less than 1% incidence
Vandetanib in VHL: Adverse Events

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>11 (32%)</td>
</tr>
<tr>
<td>Patient withdrawal</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>PI discretion/Other</td>
<td>5 (14%)</td>
</tr>
</tbody>
</table>
Goals of Therapy

• Delay/eliminate surgery
  • Induce tumor regression
  • Stabilize or slow tumor growth

• Symptom management

• Prevent metastatic spread

• Acceptable risks/side effects

Ongoing/Future Studies

- Selective VEGF receptor inhibitors
  - Pazopanib, Axitinib
  - Better toxicity profile
  - Comparable efficacy

- Novel agents

- Inclusion of CNS hemangioblastomas, pheochromocytomas
Ongoing/Future Studies

• A Pilot Trial of TKI 258 (Dovitinib) in Von Hippel-Lindau Syndrome (NCT01266070)-MD Anderson Cancer Center

• A Phase II Trial of Pazopanib in Von Hippel-Lindau Syndrome NCT01436227-MD Anderson Cancer Center
Ongoing/Future Studies

• Effect of Vorinostat on Nervous System Hemangioblastomas in Von Hippel-Lindau Disease (Missense Mutation Only) (NCT02108002)- NCI

• Bevacizumab for CNS Hemangioblastoma (NCT01015300) - Dartmouth-Hitchcock Med Ctr
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollias, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.
<table>
<thead>
<tr>
<th>Dose of Anti–PD-1 Antibody</th>
<th>Objective Response†</th>
<th>Objective-Response Rate‡</th>
<th>Duration of Response§</th>
<th>Stable Disease ≥24 wk</th>
<th>Progression-free Survival Rate at 24 wk¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients/total no. of patients</td>
<td>% (95% CI)</td>
<td>mo</td>
<td>no. of patients/total no. of patients</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Renal-cell cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>4/17</td>
<td>24 (7–50)</td>
<td>17.5+, 9.2+, 9.2, 5.6+</td>
<td>4/17</td>
<td>24 (7–50)</td>
</tr>
<tr>
<td>10.0 mg/kg</td>
<td>5/16</td>
<td>31 (11–59)</td>
<td>22.3+, 21.7+, 12.9, 12.0, 8.4</td>
<td>5/16</td>
<td>31 (11–59)</td>
</tr>
<tr>
<td>All doses</td>
<td>9/33</td>
<td>27 (13–46)</td>
<td></td>
<td>9/33</td>
<td>27 (13–46)</td>
</tr>
</tbody>
</table>

* The effective relative weight of patients in whom the response could be evaluated was initiated by label 2011 and

† The objective response rate is defined as the proportion of patients who had a complete or partial response. A complete response was defined as the disappearance of all measurable disease for at least 4 weeks. A partial response was defined as a decrease in the sum of the products of the diameters of measurable lesions by at least 30% for at least 4 weeks. A stable disease was defined as a decrease or increase in the sum of the products of the diameters of measurable lesions by at most 20% for at least 4 weeks.

‡ The objective-response rate is defined as the proportion of patients who had a complete or partial response. A complete response was defined as the disappearance of all measurable disease for at least 4 weeks. A partial response was defined as a decrease in the sum of the products of the diameters of measurable lesions by at least 30% for at least 4 weeks. A stable disease was defined as a decrease or increase in the sum of the products of the diameters of measurable lesions by at most 20% for at least 4 weeks.

§ The duration of response is defined as the time from the date of the first objective response to the date of disease progression or death from any cause, whichever occurred first.

¶ The progression-free survival rate is defined as the proportion of patients who remained progression-free for at least 24 weeks from the date of the first objective response. A patient was considered progression-free if they had not experienced disease progression or death, whichever occurred first, during the 24-week follow-up period.
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- Donna Drake
  - UOB Data Manager
- James Peterson
  - UOB Database manager
All Patients and their families
VHL Family Alliance