



**Clinical Trials in VHL:
What have we learnt
so far?**



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VHL Sunitinib Trial

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November 8, 2008
UT MD Anderson Cancer Center

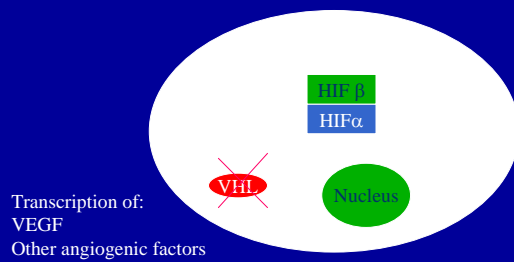
The VHL Clinical Center



- Eric Jonasch
- Louise Strong
- Douglas Evans
- Franco DeMonte
- Dan Gombos
- Molly Daniels
- Surena Matin
- Morris Groves
- Steven Waguespack
- Ian McCutcheon
- Nancy Perrier

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History?

VHL Mutation Replicates the Hypoxic State



Hypothesis

- **If** the mutation of VHL and the abnormal HIF regulation is solely responsible for the changes seen in patients,
- **Then** blockage of these changes should impact affected areas equally.

Sunitinib

- Oral agent, in pill form.
- Dosed 50mg 4 weeks on, 2 weeks off.
- Blocks a number of receptors involved in blood vessel formation: VEGFR1-3, PDGFR, c-KIT, FLT3.

MDACC Sunitinib VHL Trial

Sunitinib 50 mg
By mouth daily
4 out of 6 weeks
For 12 weeks

Respond/Stable:
Continue Sunitinib for
another 12 weeks

Progression:
Best Local
Control

MDACC Trial of Sunitinib in VHL Patients

- Endpoints:
 - Response in VHL lesions.
- Eligibility:
 - VHL patients with measurable lesions:
 - RCC between 1 and 3 cm
 - NET between 1 and 3 cm
 - Hemangioblastoma ≥ 5 mm
 - Pheochromocytomas excluded.
 - Performance status 2 or higher.
 - Not requiring imminent surgery.

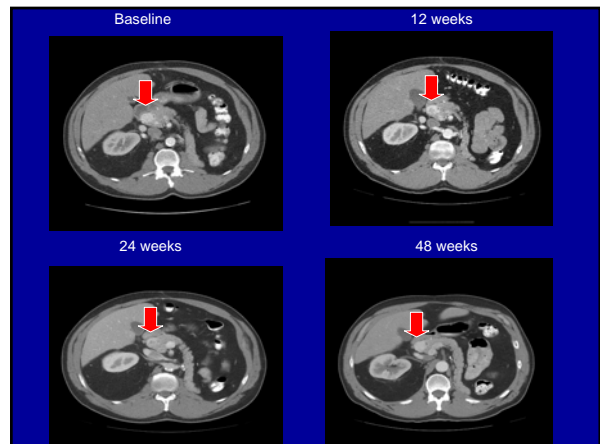
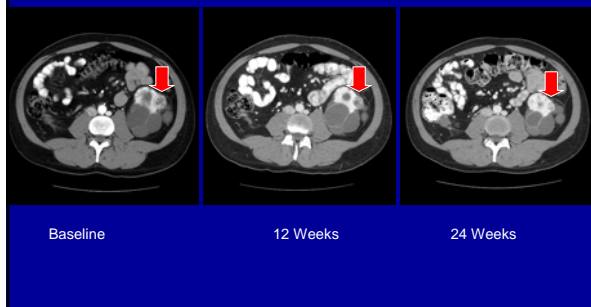
Results

- 12 patients accrued in 26 months.
- Initial accrual rate of approx 1/month declined in second year.
- 7/12 patients completed 6 months therapy:
 - 2 patients discontinued therapy voluntarily
 - 2 patients came of study because of toxicity
 - 1 patient showed progressive disease (CNS)

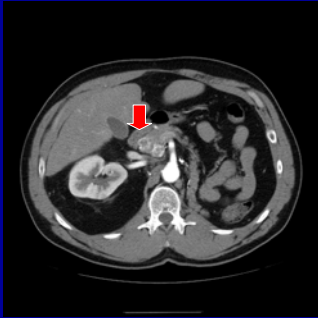
Patient Outcomes

Acc	Reason Off Study:	Type of Toxicity	Sites of Disease	Response
1	Completed therapy	Fatigue	pancreatic cysts, kidney tumors	Shrinkage of renal masses
2	Completed therapy	Fatigue	pancreas tumors, kidney cysts	Shrinkage of pancreatic masses
3	Patient choice	Fatigue	CNS, spine, kidney tumors	Shrinkage of renal masses
4	Development of toxicity	Neutropenia, back pain	Eye, CNS	Stable hemangioblastomas
5	Completed therapy	Fatigue, hand foot syndrome, diarrhea	CNS, spine, kidney tumors	Shrinkage of renal masses
6	Development of toxicity	Fatigue, hypertension	Spine, kidney cysts	Stable hemangioblastomas
7	Completed therapy	Neutropenia, fatigue, hand foot syndrome	CNS, kidney tumors, pancreatic cysts	Shrinkage of renal masses
8	Completed therapy	Fatigue, hand foot syndrome	ELST, CNS, pho?, pancreatic tumors, eye	Stable disease
9	Completed therapy	Neutropenia	CNS, kidney tumors	Shrinkage of renal masses
10	Patient choice	Hypertension, folliculitis	Eye, CNS, kidney cysts, spine	Slight decrease in cerebellar mass
11	Completed therapy	Fatigue	CNS, kidney tumors, spine	Shrinkage of renal masses
12	Disease progression		CNS	Progression in CNS

Renal Masses



Twelve months after restarting therapy



Conclusions

- Regression of cancers, but less response in hemangioblastomas.
- Sunitinib is tolerable in the majority of patients, but does show persistent and consistent toxicity.
- Recruitment has been slow in past year
 - Key barrier has been financial (trips to Houston).
 - Attempts at multicentering have met logistical barriers (high institutional costs)

Future Directions

- Complete trial accrual (n=28).
- Genotype phenotype correlations.
- Evaluate receptor expression and activation states to aid in development of next clinical trial.



For the handout . . .

- <http://vhl.org/support>
Click on "webinars"
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for individuals and families
affected with von Hippel-Lindau

VHL Family Alliance