

# Amendment

<b>Protocol Number:</b>	08C0020-H	<b>Reference Number:</b>	364849
<b>Principal Investigator:</b>	William Linehan MD NCI      UOB      301.496.6353      linehanm@mail.nih.gov		
	(NIH Employee Name, Institute/Branch, Telephone and e-mail)		
<b>Protocol Title:</b>	A Phase 2 Study of ZD6474 (vandetanib) in Patients with von Hippel Lindau Disease and Renal Tumors		

## SIGNATURES

### Principal Investigator (\*):

William Linehan MD - applied signature on 12/15/2016 8:14 PM EST

### Accountable Investigator:

PI is the Accountable Investigator

### Branch Chief/CC Department Head (\*\*):

William Linehan MD - applied signature on 12/15/2016 8:14 PM EST

### Medical Advisory Investigator (if applicable):

N/A

### Lead Associate Investigator signature:

N/A

### Referral Contact signatures:

N/A

### Associate Investigators signatures:

N/A

### For Institute/Center Scientific Review Committee:

N/A

### Other IC Clinical Director signatures:

N/A

## APPROVALS

### IRB Chair:

Michael Hamilton - applied signature on 01/12/2017 2:42 PM EST

### Clinical Director:

N/A

## CONCURRENCE

OPS Protocol Specialist:

Michelle Lanham	AM   H	01/24/17
Signature	Print Name	Date

\* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

\*\* I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/ gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

<b>IRB Meeting Date:</b>	Expedited
<b>DEC Clearance Date:</b>	11/17/2016
<b>Protocol Version Date:</b>	11/16/2016

**Abbreviated Title:** Phase II of ZD6474 in VHL

**NCI Protocol Number:** 08-C-0020

**Version Date:** November 16, 2016

**Amendment:** H

A Phase II Study of ZD6474 (Vandetanib) in Patients with Von Hippel Lindau Disease and Renal Tumors

**NCI Principal Investigator:** W. Marston Linehan, M.D. <sup>A, B, C, D, E, F</sup>  
Branch Chief, UOB, CCR, NCI  
10 Center Drive  
10/1-5942  
Tel: 240-760-6245  
Email: [linehanm@mail.nih.gov](mailto:linehanm@mail.nih.gov)

**NIH Lead Investigator:** Ramaprasad Srinivasan, M.D., Ph.D. <sup>A, B, C, D, E, F</sup>  
Staff Clinician, UOB, CCR, NCI  
10 Center Drive  
10/2-5950  
Tel: 240-760-6251  
Email: [Ramaprasad.Srinivasan@nih.gov](mailto:Ramaprasad.Srinivasan@nih.gov)

**Statistician:** Joanna H. Shih, Ph.D., BRB, DCTB, NCI <sup>E, F</sup>

**NIH Associate Investigators:** Peter Pinto, M.D., UOB, CCR, NCI <sup>A, B, C, D, E, F</sup>  
Martha Ninos, R.N., OCD, CCR, NC <sup>A, B, C, E, F</sup>  
Julia Friend, P.A.-C., UOB, CCR, NCI <sup>A, B, C, D, E, F</sup>  
Geri Hawks, R.N., OCD, CCR, NCI <sup>A, B, C, E, F</sup>  
Jane Trepel, DTB, CCR, NCI <sup>E, F</sup>  
Douglas Rosing, M.D., Cardiology, NHLBI <sup>A, B, E, F</sup>  
Dave Kohler, Pharm.D., CC Pharmacy <sup>B, E</sup>  
Heidi Kong, M.D., DERM, CCR, NCI <sup>A, B, C, D, E, F</sup>

**Referral Contact/  
Study Coordinator:** Geri Hawks, R.N., OCD, CCR, NCI  
10 Center Drive  
Building 10 CRC, Room 2-5750  
Bethesda, MD 20892-1208  
Phone: 240-760-6244  
Email: [ghawks@mail.nih.gov](mailto:ghawks@mail.nih.gov)

- A. Obtain information by intervening or interacting with living individuals for research purposes*
- B. Obtaining identifiable private information about living individuals*
- C. Obtaining the voluntary informed consent of individuals to be subjects*
- D. Makes decisions about subject eligibility*
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
- G. Some/all research activities performed outside NIH*

**Investigational Agent:**

Drug Name:	ZD6474
IND Number:	78,970
Sponsor:	W. Marston Linehan, M.D.

## **PRÉCIS**

### **Background:**

- Von Hippel Lindau disease is a hereditary cancer syndrome in which affected individuals are at risk for developing tumors in a number of organs, including the kidneys, brain, spine, adrenal glands, eyes and pancreas.
- The molecular hallmark of VHL is inactivation of the VHL gene which leads to accumulation of proteins targeted for degradation through the ubiquitin pathway, which includes a group of transcriptionally active proteins called the hypoxia inducible factors (HIF), whose alpha subunits undergo degradation in a VHL-dependent fashion. Accumulation of HIFs results in overexpression of several genes including VEGF, GLUT-1, TGF- $\beta$  PDGF, and erythropoietin, which are believed to play a role in tumorigenesis, tumor progression and metastasis.
- ZD6474 is an orally administered receptor tyrosine kinase inhibitor with activity against the Kinase insert domain-containing receptor/vascular endothelial growth factor receptor 2 (KDR/VEGFR2) and the epidermal growth factor receptor (EGFR). KDR/VEGFR2 is an endothelial cell receptor for vascular endothelial growth factor (VEGF) and plays a crucial role in mediating tumor angiogenesis, while EGFR (a receptor for TGF- $\beta$  and EGF) is believed to mediate tumor growth and proliferation.

### **Objective:**

#### Primary Objective

- To assess the overall response rate in VHL patients with renal tumors treated with single agent ZD6474

### **Eligibility:**

- Adults with clinical diagnosis of von Hippel Lindau disease
- Presence of one or more measurable renal tumors
- Age  $\geq$  18 years
- Adequate organ function, performance status (ECOG 0-2) and life expectancy ( $>3$  months)

### **Design:**

- Single agent ZD6474 administered daily at a starting dose of 300mg/day
- Patients will be evaluated for response every 12 weeks using RECIST criteria
- The study is based on an open label two-stage optimal phase II design
- Accrual of a maximum of 37 patients

## TABLE OF CONTENTS

1	INTRODUCTION .....	6
1.1	STUDY OBJECTIVES .....	6
1.2	Background and Rationale .....	6
2	ELIGIBILITY ASSESSMENT AND ENROLLMENT .....	18
2.1	Eligibility Criteria .....	18
2.2	Research Eligibility Evaluation .....	21
2.3	Registration Procedures .....	21
3	STUDY IMPLEMENTATION .....	22
3.1	Study Design .....	22
3.2	Study Drug Administration .....	23
3.3	Dosing Delays/Dose Modifications .....	23
3.4	Research Studies .....	28
3.5	Study Evaluations And Schedule .....	30
3.6	Study Calendar .....	32
3.7	Concurrent Therapies .....	33
3.8	Surgical Guidelines .....	33
3.9	Off Study Criteria/Off Treatment Criteria .....	33
3.10	Post-Treatment Follow-up .....	33
4	SUPPORTIVE CARE .....	33
5	DATA COLLECTION AND EVALUATION .....	34
5.1	Data Collection .....	34
5.2	Response Evaluation .....	34
5.3	Toxicity Criteria .....	39
6	STATISTICAL SECTION .....	39
6.1	Two-stage Design .....	39
6.2	Response Frequency .....	39
6.3	Accrual Ceiling .....	40
7	HUMAN SUBJECTS PROTECTION .....	40
7.1	Rationale for Subject Selection .....	40
7.2	Evaluation of benefits and risks/discomforts .....	40
7.3	Risk/Benefit relationship .....	41
7.4	Consent and assent processes and documents .....	41
7.5	Patient records and quality assurance .....	41
8	SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN .....	42
8.1	Definitions .....	42
8.2	NCI-IRB and NCI Clinical Director (CD) Reporting .....	45
8.3	FDA Reporting Criteria .....	45
8.4	DATA AND SAFETY MONITORING PLAN .....	47
9	COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT CRADA)/CLINICAL TRIALS AGREEMENT (CTA) .....	47
10	PHARMACEUTICAL INFORMATION .....	48
10.1	Source .....	48
10.2	Solubility .....	49
10.3	Mode of Action .....	49

10.4	Formulation and Preparation .....	49
10.5	Composition.....	49
10.6	Stability and Storage .....	50
10.7	Dosage and Administration.....	50
10.8	Reported Adverse Events and Potential Risks .....	50
10.9	Potential Drug Interactions .....	50
10.10	Availability .....	50
10.11	Agent Ordering.....	50
10.12	Agent Accountability .....	51
11	REFERENCES.....	52
12	APPENDICES .....	55
12.1	Appendix A: ecog performance status.....	55
12.2	Appendix B: New York Heart Association (NYHA) Cardiac Classification .....	56
12.3	Appendix C: Medications Known To Prolong The QT Interval And/Or Induce Torsades De Pointes (Tdp) (Updated 19 August 2011) .....	57
12.4	Appendix D: List of drugs interacting with CYP3A4.....	61
12.5	Appendix E: Diagnostic criteria for von hippel-lindau .....	64

## **1 INTRODUCTION**

### **1.1 STUDY OBJECTIVES**

#### **1.1.1 Primary Objective**

- To assess the overall response rate in VHL patients with renal tumors treated with single agent ZD6474

#### **1.1.2 Secondary Objectives:**

- To study the safety and tolerability of ZD6474
- To evaluate time to progression and progression-free survival in VHL patients receiving ZD6474
- To study the effect of ZD6474 treatment on non-renal tumors associated with von Hippel Lindau disease (pancreatic tumors, pheochromocytoma, CNS hemangioblastomas)
- To investigate the effect of ZD6474 on circulating endothelial cells and endothelial progenitor cells and to explore the utility of these markers as surrogates of angiogenesis inhibition
- To investigate the effect of ZD6474 on biomarkers of angiogenesis such as plasma VEGF and soluble VEGFR2

### **1.2 BACKGROUND AND RATIONALE**

#### **1.2.1 von Hippel Lindau Disease**

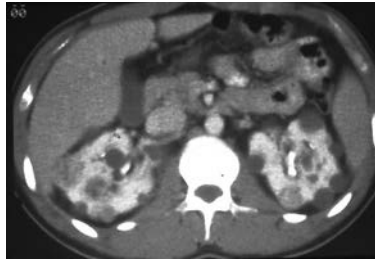
Von Hippel Lindau disease is a hereditary cancer syndrome transmitted in an autosomal dominant fashion. The underlying defect is a germline mutation in the VHL gene, which places affected individuals at risk for developing tumors in a number of organs, including the brain, spine, kidneys, adrenal glands, eyes and pancreas (1-6). The incidence of VHL is approximately one in 36,000 live births (1,7).

#### **1.2.2 VHL Clinical Manifestations**

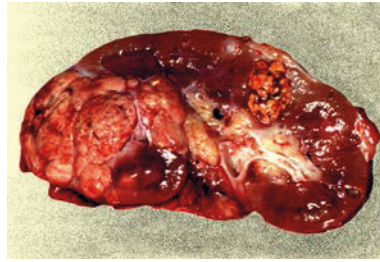
Bilateral, multifocal clear cell renal carcinoma  
CNS Hemangioblastomas (Cerebellum, Spine)  
Pancreatic neuroendocrine tumor and cysts  
Pheochromocytomas  
Retinal angiomas  
Endolymphatic sac tumors

#### ***Renal Tumors in VHL***

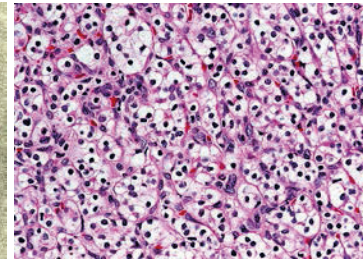
Affected individuals in VHL kindreds are at risk for the development of bilateral, multifocal clear cell renal carcinoma (1-5).



**VHL bilateral, multifocal RCC**



**VHL Renal Tumor**



**Clear Cell RCC**

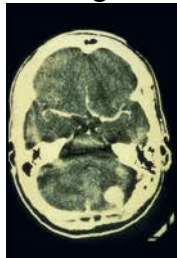
While these tumors can present as localized tumors, they can grow and metastasize. Historically, 35-45% of VHL patients died of metastatic renal cell carcinoma.



VHL patient who presented with a large renal mass (left) and pulmonary metastases from the clear cell renal carcinoma

*Non-renal tumors in von Hippel Lindau disease*

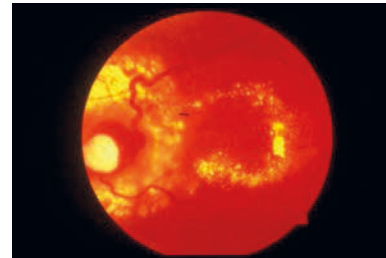
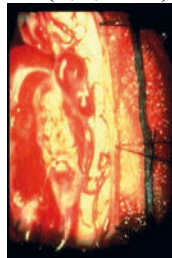
1) VHL patients are at risk for the development of CNS tumors (cerebellar and spinal hemangioblastomas) and retinal angioma (4,5,8-12)



**Cerebellar HB**

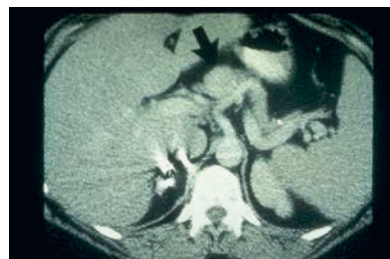


**Spinal Hemangioblastoma**



**Retinal Angioma**

2) These individuals are also at risk for the development of pancreatic cysts and neuroendocrine tumors (13-17).



**Pancreatic neuroendocrine tumor**

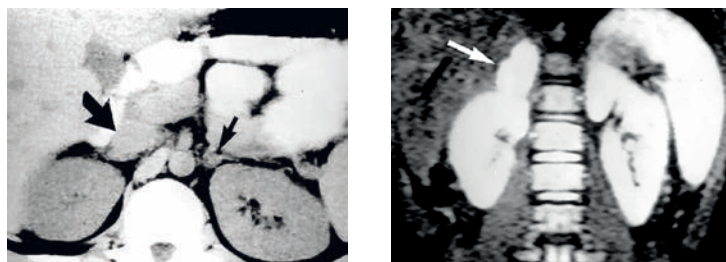


**VHL pancreatic cysts**

The pancreatic neuroendocrine tumors are malignant and can metastasize.

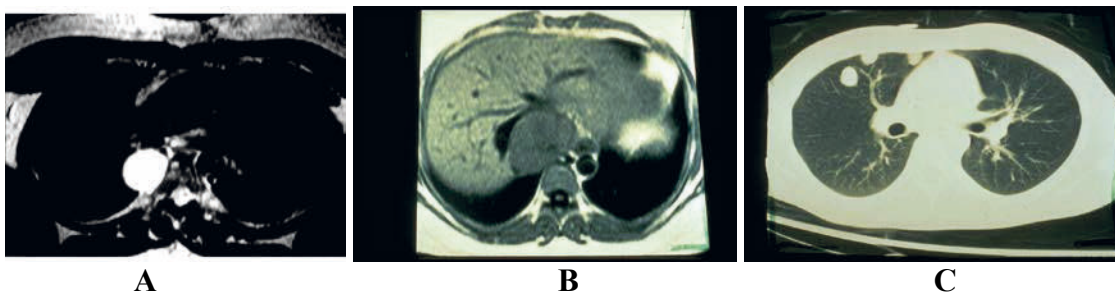


3) These patients are also at risk for the development of pheochromocytomas which can occur at an early age (18).



Abdominal CT scan (left) and MRI scan (right) reveal the presence of bilateral pheochromocytomas in a 10 year old boy.

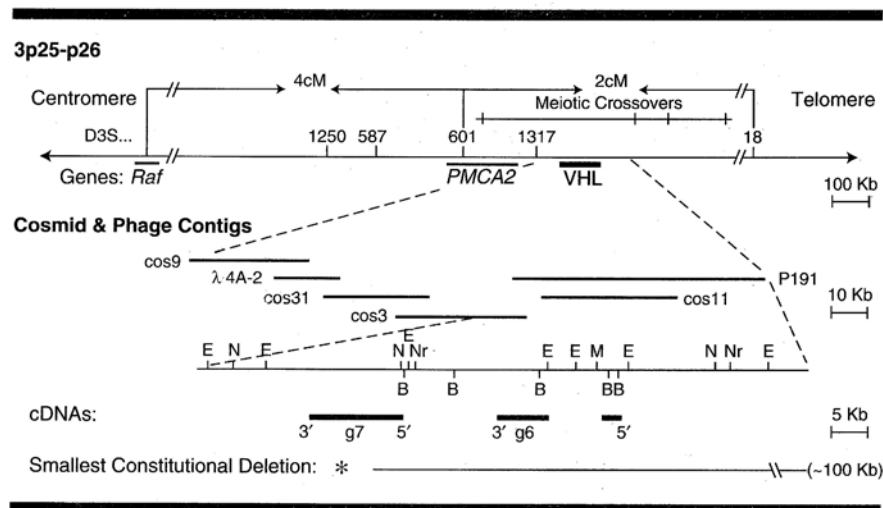
VHL pheochromocytomas can occur at adrenal or extra-adrenal sites and, although the pheochromocytomas are usually benign, they can be can be lethal. They can also be malignant and can metastasize.



**VHL associated pheochromocytomas can be extra-adrenal. Panel A shows a pulmonary pheochromocytoma in a VHL patient. These tumors can also be malignant. Panel B shows a large retroperitoneal, recurrent malignant pheochromocytoma that had spread to the lungs (Panel C) in a 24 year old female.**

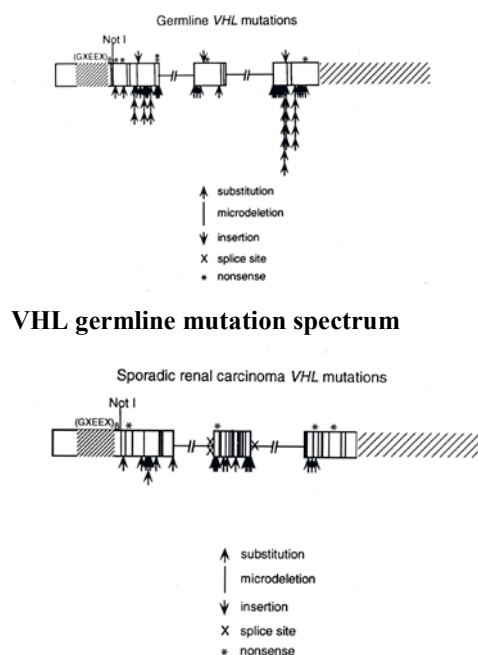
### 1.2.3 The VHL Tumor Suppressor Gene

By studying VHL kindreds here at the NCI we were able to identify the VHL gene (19). The gene is located on the short arm of chromosome 3 (3p25-26). VHL is a classical tumor suppressor gene and tumorigenesis due to VHL inactivation conforms to Knudson's 'two-hit' hypothesis (20). The gene has three exons that encode the VHL protein (19). Two isoforms of the VHL protein have been described. Full length VHL protein has 213 amino acids and localizes to the nucleus as well as the cytoplasm. A truncated form, resulting from translation initiation at codon 54, has also been characterized and appears to be functionally active (21,22).



Genetic linkage analysis at the NCI resulted in the identification of the G7 VHL cDNA, which turned out to be the VHL gene.

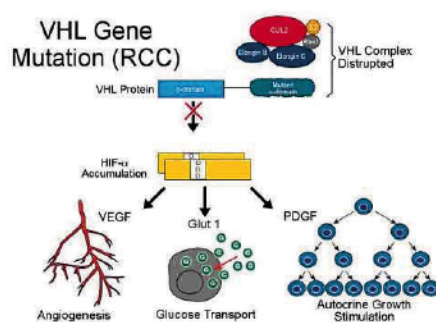
We and others have shown that this gene is also the gene for the common form of sporadic renal cell carcinoma (viz., clear cell RCC).



### ***VHL mutations: Functional and Biologic consequences***

While VHL mutations were initially identified as the genetic basis of von Hippel Lindau disease, inactivation of the gene by mutation or promoter hypermethylation has also been described in a high proportion of sporadic clear cell renal cancers. VHL protein forms a complex with other cellular proteins including elongins B and C, and Cullin 2 (the VCB-CUL2 complex) (23). This complex plays an important role in the degradation of cellular proteins via the ubiquitin pathway. Inactivation of VHL consequently leads to accumulation of proteins targeted for degradation through this pathway. This includes a group of transcriptionally active proteins called the

hypoxia inducible factors (HIF), whose alpha subunits undergo degradation in a VHL-dependent fashion (24). Accumulation of HIFs results in overexpression several genes including VEGF, GLUT-1, TGF- $\beta$ , PDGF, and erythropoietin (1-4). VEGF is an important regulator of tumor angiogenesis and hence is implicated in tumor growth and progression. VEGF exerts its activity through several receptor tyrosine kinases expressed on endothelial cells, chief among them being the fms-like tyrosine kinase-1/VEGF receptor 1 (Flt-1/VEGFR1) and the kinase insert domain containing receptor/VEGF receptor 2 (KDR/VEGFR2) (25). In addition to promoting angiogenesis in the tumor microenvironment, VHL inactivation can also directly promote tumor growth via the autocrine and paracrine effects of TGF- $\beta$  and PDGF, which act through receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR, a ligand for TGF- $\alpha$ ) expressed on tumor cell surface. Thus VHL inactivation initiates a series of downstream events that promote tumor progression.



**VHL gene pathway**

#### 1.2.4 Treatment for VHL-associated tumors

Although a variety of systemic treatment options including cytokines (IL-2, IFN) as well as newer targeted anti-angiogenic agents (e.g. sunitinib, sorafenib) are available for patients with sporadic metastatic clear cell RCC, these agents have not been evaluated in the management of VHL associated RCC. Consequently, the treatment approach for VHL associated renal tumors remains surgical and involves resection of tumors that have reached a size of approximately 3 cm.

We have estimated that affected VHL individuals may develop up to 600 tumors per kidney (26). Over the past 15 years we have observed patients with VHL-associated renal cancer until their tumors grew to 3 cm in diameter, whereupon nephron-sparing surgery is recommended. This strategy is used to increase time between operations and decrease patient morbidity. With this treatment approach, we have followed 96 von Hippel-Lindau (VHL) patients for a median of 60 months. No patient with maximum renal tumor diameter less than 3 cm has developed metastases (27,28). Tumor diameters greater than 3 cm are associated with increasing frequency of metastases. There is no effective standard therapy for VHL patients with metastatic renal cancer. Historically 35-45% of patients affected with VHL have died of metastatic renal carcinoma. Currently, tumors of non-renal origin are similarly managed by surgical resection to relieve symptoms or circumvent potentially dangerous sequelae (29,30) (for e.g. CNS hemangioblastomas, pheochromocytomas) or diminish metastatic potential (31) (e.g. pancreatic neuroendocrine tumors).

### 1.2.5 ZD6474

ZD6474 is an orally administered receptor tyrosine kinase inhibitor with potent activity against VEGFR2 as well as activity against EGFR (32,33).

Murine preclinical human xenograft models have demonstrated activity of ZD6474 against a variety of tumors including those arising in the lung, prostate, ovary, breast and colon. Reduction in tumor blood flow, vascular density and vascular permeability have been seen in a mouse xenograft model, suggesting inhibition of the VEGF pathway by the drug (34). The following is a summary of pre-clinical and clinical studies with ZD6474:

#### **In vitro studies (34)**

In isolated enzyme assays, ZD6474 was found to be a potent inhibitor of KDR tyrosine kinase activity ( $IC_{50}=40nM$ ), with additional activity against Flt-4 ( $IC_{50}=110nM$ ) and EGFR ( $IC_{50}=500nM$ ). Less potent activity was seen against a range of other tyrosine kinases including PDGFR, Tie-2, FGFR1, MEK, CDK2, c-kit, ErbB2, FAK, PDK-1, AKT and IGF-1R, with  $IC_{50}$  ranging from  $1\mu M$  to  $>200\mu M$ .

ZD6474 inhibited the proliferation of both VEGF-stimulated and EGF-stimulated HUVEC cell lines ( $IC_{50}=60nM$  and  $170nM$ , respectively), while basal HUVEC proliferation was not significantly affected. When co-cultured with human fibroblasts, endothelial tube formation by HUVEC cells was inhibited at similar concentrations of ZD6474. Direct inhibition of tumor growth was demonstrated against established lung, colon, ovarian, breast, and prostate cancer cell lines, but only at higher concentrations, with  $IC_{50}$ s in the 0.6 to  $13.5\mu M$  range.

The effect of ZD6474 on cardiovascular function has been investigated in vitro using the human ether-a-go-go gene assay as well as by assessment of action potential parameters recorded from canine Purkinje fibres. A concentration dependent increase in action potential duration was seen in these assays.

The parent compound as well as the N-oxide and N-desmethyl metabolites were active in the above assays.

#### **Pre-clinical studies**

##### *Pharmacokinetic Studies and metabolism*

Pharmacokinetic studies were performed in rats and dogs. In both species,  $>50\%$  of the drug was absorbed when administered orally. Time to peak plasma concentration was 3-8 hours. Plasma clearance was rapid and was greater in male than in female rats. The drug was rapidly and extensively distributed with apparent volumes of distribution of approximately  $30L/kg$  in both male and female rats. The highest concentrations were found in the GI tract, liver, adrenal glands, Harderian glands, pituitary, spleen and pigmented tissue. Delayed clearance from adrenal, kidney and testes was observed. The terminal half life was estimated at 16b hours in male and 31 hours in female rats, and at 8.27 hours in dogs. The drug is eliminated both by biliary excretion and in urine. Two metabolites have been identified in samples from rats and dogs- the N-oxide of ZD6474 and the N-desmethyl of ZD6474.

ZD6474 underwent minimal metabolism in rat and dog hepatocytes and no metabolism in human hepatocytes or human microsomes. No inhibitory effects on the activity of human P450 isoenzymes CYP1A2, 2C9, 2C19 or 3A4 were observed but the drug inhibited activity of CY 2D6.

Plasma protein binding ranged from 83% in the rat to 90% in human. ZD6474 was found to bind both human serum albumin and alpha-1-glycoprotein.

#### *Toxicology*

Single oral doses of 2000mg/kg in mice and rats were not tolerated. A single oral dose of 1000mg/kg was tolerated in rats and produced premature death in 1/10 mice. A single IV dose of 50mg/kg induced early death in 1/10 mice. The following organ-specific toxicities were seen in multiple-dose studies:

- Dose-related dysplasia of the epiphyseal growth plates of the femoro-tibial joint was seen in rats receiving 25-75mg/kg/day and in dogs dosed at 40mg/kg/day by one month.
- Elevated ALT, AST and LDH as well as histopathologic changes consistent with hepatocellular necrosis and acute cholangitis were seen in the one-month rat study at a dose of 75mg/kg/day. Death from acute cholangitis was seen in rats receiving 20mg/kg/day in the 6-month study. These changes were not observed with the one-month or nine-month dog studies.
- Gastro-intestinal toxicity in the form of emesis, diarrhea and weight loss was observed in the 1 and 9-month dog studies. No accompanying histopathologic changes were noted, and the toxicity was reversible on cessation of drug use.
- Renal papillary necrosis was seen in the rat 1-month study at doses of 25-75mg/kg/day
- Decreased numbers of corpora lutea, increased post-implantation loss, embryofetal loss, delayed fetal development, heart vessel abnormalities, and precocious ossification of skull bones reflect the range of reproductive and embryofetal toxicity observed in rats
- Reversible histopathologic and ultrastructural changes consistent with phospholipidosis was seen in the rat 1-month and 6-month studies, but were not observed in the dog studies
- Reversible, dose-related acute folliculitis and epidermal microabscess formation in the muzzle region of skin was noted in both the 1-month and 6-month rat toxicity studies
- In dog studies, following single oral doses of 5, 15, or 40mg/kg, an increase in heart rate 75-360 minutes following the largest dose was observed. In the dose range studies, no clear effects on blood pressure, PR interval, QRS duration, RR interval, QT interval, waveform or rhythm were seen

#### *Biologic Effects and efficacy against tumors*

The following effects consistent with VEGF inhibition were seen in animal studies:

- When administered at a dose of 50mg/kg to Alderley Park rats, ZD6474 inhibited the hypotension normally induced by administration of bolus VEGF
- Dose-dependent increases in the hypertrophic chondrocyte zone of the epiphyseal growth plates of growing rats were seen



- ZD6474 inhibited tumor-associated angiogenesis in athymic mice intradermally implanted with A549 lung cancer cells
- ZD6474 inhibits tumor vascular flow, volume and permeability as assessed by K trans measurements in established PC-3 prostate tumor xenografts using dynamic contrast-enhanced MRI
- Antitumor activity
  - In human tumor xenograft models (lung, prostate, ovary, breast, vulval, colon), ZD6474 inhibited the growth of established subcutaneous tumors in mice
  - Tumor regression was observed in established PC-3 prostate tumor xenografts, but not in a Calu-6 (lung) tumor xenograft model
  - In murine spontaneously metastatic tumor models (melanoma and renal cell cancer) administration of ZD6474 reduced both primary tumor growth and the incidence of pulmonary metastases
  - Anti-tumor effects of ZD6474 were also identified in a human colon tumor xenograft in athymic rats and in two syngeneic tumor models (melanoma, lung) in immunocompetent mice
  - Inhibition of angiogenesis as evidenced by changes in microvascular architecture was seen in a murine orthotopically implanted renal cell cancer model (35).

## **Human Studies (34, 36)**

### **Phase I Studies:**

Several phase I trials have been conducted in human subjects. Trial 6474IL/0001 (Western study) was conducted as a multicenter, dose escalation phase I trial evaluating 50, 100, 200, 300, 500 and 600mg doses administered orally as a daily single dose. A total of 77 patients have been treated on this trial at various dose levels, including an expanded cohort of 19 and 25 patients respectively at the 100mg and 300mg dose levels who were enrolled to better evaluate the effect of ZD6474 on QT interval and ST, T wave changes. A second phase I trial conducted in Japan (TVE-15-11) followed a dose escalation pattern evaluating 100, 200, 300 and 400mg daily oral doses. A total of 18 patients have been accrued on this trial.

### *Pharmacokinetics*

Pharmacokinetic data obtained from the Western and Japanese studies were comparable. Absorption was highly variable, with individual patients having a T<sub>max</sub> as late as 24 hours post-dose. Following achievement of maximum plasma concentration, C<sub>max</sub> declined in a biphasic manner. Terminal half-life was estimated to be about 4-5 days and appeared to be independent of dose. Both mean AUC and C<sub>max</sub> increased with increasing dose in a linear manner with about 2 to 6 fold in inter-individual variability in AUC for a given dose. A comparison of the mean weekly trough levels suggest that steady state was achieved by day 29, with marked accumulation between day 1 and 29.

### *Adverse Events*

The most common adverse events seen on both trials were:

- 1) Rash- At least 2 distinct types of rash were seen- A macular erythema and a follicular (acneiform) rash. Rash was reported in 54 (72%) patients in the Western and 14 (77.8%) patients in the Japanese study. The occurrence of rash appeared to be dose-dependent.

- 2) Gastrointestinal toxicity- Diarrhea was reported in 42 (56%) of the Western patients and 10 (56%) of the Japanese patients. Other common GI side effects seen the western and Japanese studies included nausea (39% in the Western and 22% in the Japanese studies), vomiting (22% and 17% respectively), anorexia (29% and 28% respectively) and constipation (24% in the Western study).
- 3) Central Nervous System- Headaches were reported by 19 (25%) patients and dizziness by 14 (17%) patients in the Western study. 27% of the patients in the Japanese study reported headaches.
- 4) Cardiovascular toxicity-
  - a. In the western trial, 6 patients (8%) had T-wave or ST-segment changes consistent with repolarization abnormalities.
  - b. QT/QTc prolongation- In the Western study, in the initial 49 patients enrolled, QTc prolongation occurred in 0 of 9 patients at 50mg, 1 of 8 patients at 100mg, 2 of 8 patients at 200mg, 1 of 8 patients at 300mg, 2 of 8 patients at 500mg, and 1 of 8 patients at 600mg. The protocol was subsequently amended to include 11 additional patients at the 100mg dose level and 12 patients at the 300mg dose level, along with the use of extensive ECG monitoring to assess QTc prolongation. In the expanded cohorts, 1/11 patients at the 100mg dose level and 2/12 patients at the 300mg dose level had QTc prolongation. In the Japanese study, 11/18 patients (61%) developed QTc prolongation. A PK-PD correlation for QTc prolongation appears to exist. The relationship is best described by a direct linear effect model with a concentration of 1ng/ml causing an increase of 0.0243 ms in QTc interval. None of the QTc prolongations were considered to symptomatic
  - c. Hypertension- Hypertension was seen in 21% of the patients in the two trials and on average involved a 5mm Hg increase in mean arterial pressure.

Other commonly occurring adverse events (occurring in >10%) include: Fatigue (36%), abdominal pain (35%), back pain (15%), fever (14%), cough (14%), peripheral edema (12%), insomnia (12%), hematuria (11%), dyspnea (11%), proteinuria (11%).

#### *Dose limiting toxicity*

In Trial 6474IL/0001, dose levels of 50, 100, 200, 300, 500 and 600 mg/day were evaluated. At 600 mg/day, 3 of 8 patients developed dose limiting toxicity (DLT): thrombocytopenia, and diarrhea. Because the plasma levels of ZD6474 observed in subjects in the 500 mg overlapped considerably with those at 600 mg, it was concluded that doses to take forward into later phases of development were less than 500 mg.

In Trial TVE-15-11, dose levels of 100, 200, 300 and 400 mg/day were evaluated. DLT was seen in 2 of 3 subjects in the 400 mg/day cohort (increased alanine aminotransferase and hypertension) and 2 of 6 subjects in 300 mg/day cohort (grade 3 diarrhea, hypertension, and headache in one patient, and grade 2 rash lasting longer than 7 days in a second subject).

Therefore, in both trials a dose of 300 mg/day was identified as the highest well-tolerated dose of ZD6474.

#### *Withdrawal from Study*

67 patients were withdrawn from study in the 6474IL/0001 trial. 56 of these withdrawals were a

result of disease progression. 6 patients were withdrawn from study due to adverse events. One patient was withdrawn because of a rash, one patient due to fatigue, one due to folliculitis, and one patient was withdrawn on account of abdominal pain. A 72 year old female with colorectal cancer and pre-existing hypertension and edema developed congestive heart failure and was withdrawn from study as a consequence. The etiology of the heart failure is unclear and a contribution from ZD6474 cannot be ruled out. One patient was withdrawn from protocol due to abnormal QTc prolongation. 3 patients withdrew consent and were taken off study consequently.

In the Japanese study, 5/18 patients were withdrawn from study due to disease progression. In addition, one patient with QTc prolongation and one with dose limiting alanine aminotransferase elevation were withdrawn.

### *Efficacy*

#### Phase I study results

Two phase I studies have been completed in the West and Japan (6474IL/0001 and 6474JP/0001), in which 90 (72 Western and 18 Japanese) patients with malignant tumors have been exposed to ZD6474 (50 to 600 mg). By the end of July 2002, safety data were available from 70 patients (40 males and 30 females). Cohorts received doses ranging from 50 mg/day to 600 mg/day in the Western phase I study and from 15 patients receiving doses ranging from 100 mg/day to 400 mg/day (9 males and 6 females) in the Japanese trial. In the Japanese Phase I trial, nine patients with non-small cell lung cancer (NSCLC) who were heavily pre-treated and failed all prior therapy regimens (seven adenocarcinomas, one squamous cell, and one carcinoma not otherwise specified) were treated with ZD6474; four achieved partial response at doses ranging from 200 to 300 mg. This suggests that ZD6474 may have activity as monotherapy in otherwise chemoresistant NSCLC. Testing this agent in other tumors in light of these results is appropriate.

#### Summary

The data from the Phase I studies confirm that ZD6474 is safe for further study in patients with cancer. Dose limiting toxicity in greater than 33% of patients was observed at doses above 300 mg in both the Western and Japanese Phase I trials. Plasma concentrations of ZD6474 achieved at steady state with 300 mg cover the theoretical IC<sub>50</sub> and KDR as extrapolated from in vitro data in the VEGF-stimulated umbilical vein endothelial cells in 100% of patients. A dose of 300 mg, with options for stepwise dose reductions to ensure tolerability, is therefore recommended. The clinical effect of ZD6474 was shown in preliminary results from the Phase I study in Japan, in four of nine patients with NSCLC who received up to 300 mg of ZD6474 had objective responses as evaluated by radiographic studies.

#### **Phase II Studies:**

Several phase II studies are either currently in progress or have been completed.

Two Phase II studies in NSCLC with ZD6474 have been completed. A randomized double blind Phase II trial comparing ZD6474 monotherapy with gefitinib monotherapy in 168 patients with advanced NSCLC as second or third line therapy demonstrated that patients receiving ZD6474 300mg had a statistically significant prolongation of progression free survival (PFS) compared with gefitinib 250mg, with a mean PFS of 11.0 weeks and 8.1 weeks respectively. The adverse event profile of ZD6474 was similar to that seen in previous trials, and included diarrhea (CTC



grade 3/4, 8.4%), rash (CTC grade 3/4, 4.8%) and asymptomatic QTc prolongation (all CTC grade 1, 20.5%). A higher incidence of cardiac, gastrointestinal and respiratory serious adverse events was noted in the ZD6474 arm compared with the gefitinib arm, although it is unclear if this increase can be attributed to ZD6474 (37)

Another randomized double blind Phase II study evaluated PFS in second-line treatment of 127 patients with advanced NSCLC, and demonstrated that ZD6474 100mg or 300mg plus docetaxel increased median PFS to 19 weeks and 17 weeks respectively, compared with 12.0 weeks for docetaxel plus placebo (38). While toxicities were similar to those expected in patients treated with docetaxel and those observed in other ZD6474 studies, the ZD6474 arm had more serious adverse events compared to the docetaxel/placebo arm.

In an ongoing randomized double-blind phase IIa dose-finding study in 53 Japanese patients with NSCLC were given ZD6474 as monotherapy, at doses of 100, 200 or 300 mg/day. Interim results demonstrated a 11% PR rate and a 51% disease control rate (PR+CR+stable disease) (39). The toxicity profile was similar to that seen in other trials with ZD6474, although the investigators reported a death related to interstitial lung disease that was considered to be related to ZD6474. Also reported was a case of cerebellar hemorrhage in a patient receiving the 200mg dose.

Results from a phase II trial to assess objective tumor response in patients with hereditary metastatic medullary thyroid cancer having mutations in the RET protooncogene receiving ZD6474 monotherapy (300mg/day) were recently reported (40). Three of sixteen patients enrolled had a partial response, while an additional ten patients demonstrated stable disease >8 weeks. A >50% reduction in serum tumor markers (calcitonin) was observed in 12 patients. Based on these promising data, a randomized phase II study of ZD6474 vs placebo in patients with advanced medullary thyroid cancer is currently being planned.

### **Emerging Safety Profile/ Composite List of Adverse Events**

Notable and/or frequent side effects associated with the above phase I and phase II studies have been described along with each study. The following is a system-wise list of adverse events encountered on all completed or currently accruing studies as summarized in the most current Investigators' Brochure (version 9) provide by the drug sponsor.

Reported adverse events that may be related to vandetanib are listed below by body system.

- Cardiovascular
  - ☐ Abnormal ECG (with or without QT prolongation; ie, either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes, ventricular tachycardia, and hypertension
- ☐ Central Nervous System
  - ☐ Headache or dizziness
  - Reversible posterior leukoencephalopathy syndrome
  - Hydrocephalus
- ☐ Digestive

- ☐ Constipation, diarrhea, non-specific abdominal pain, nausea, gastroesophageal reflux, stomatitis esophageal candidiasis, vomiting, and biliary or bowel obstruction or perforation, pancreatitis, enteritis, colovesical fistula
- Haematologic and lymphatic
  - ☐ Ecchymosis, anemia, neutropenia, and thrombocytopenia
- ☐ Investigations/Laboratory
  - ☐ Elevated liver function tests, generally CTC/CTCAE grade 1-2. Preliminary data suggests these are reversible, in some cases even while continuing therapy.
- ☐ Metabolic and nutritional
  - ☐ Anorexia, dehydration, hypokalaemia, hypomagnesaemia, hypercalcemia and hypophosphataemia
- ☐ Skin and appendages
  - ☐ Acneiform rash, pruritus, macular or maculopapular rash (generalised or localised), localised and generalised erythema, photosensitivity reaction, and sweating. On occasion, especially when given with chemotherapy, these have progressed to more serious conditions, including exfoliative dermatitis, skin desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, erythema multiforme and necrotizing fasciitis.
  - Wound healing complications
  - Hand-foot syndrome
- ☐ Respiratory
  - ☐ Interstitial lung disease, pulmonary effusion and pneumonia. A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough because of inflammation or scar tissue formation in the lungs, although this could be due to the underlying lung cancer.
- ☐ Renal
  - ☐ Proteinuria, haematuria and renal failure.
- ☐ Vascular
  - ☐ Arterial ischaemic events (including myocardial infarction, stroke, peripheral ischaemia), venous thromboembolism (including pulmonary embolism). A small number of patients receiving vandetanib have developed blood clots affecting the legs or lungs. This may have been due to the patient's cancer or other illness at the time; however, it is considered possible that vandetanib might increase the risk for developing blood clots.
  - Intracranial bleeding
- Psychiatric
  - ☐ Mood disorders (anxiety, depression, insomnia). It is possible that these events are not direct effects of vandetanib, but rather are secondary to symptoms of cancer or to other effects of vandetanib (rash, etc).
- Ophthalmologic
  - ☐ Corneal changes, including ulceration
- ☐ General
  - ☐ Asthenia, fever, weight loss, pain, and fatigue

In addition, a number of other side effects have been reported in clinical trials using ZD6474 alone, in combination with other chemotherapy agents or radiation. It is unclear whether these side effects are related to ZD6474, or are caused by other factors (such as chemotherapy or

radiation). These side effects include:

- Infections, including life-threatening bacterial infections
- Seizures and facial nerve palsies
- Syncope
- LV dysfunction
- Respiratory failure
- Esophageal fistula

Hemorrhage from both tumor and non-tumor sites have been described with several agents targeting the VEGF pathway (such as sunitinib, sorafenib, bevacizumab etc.). Episodes of bleeding with the above agents have been occasionally life-threatening or fatal. Experience with anti-VEGF agents in VHL patients is limited and largely anecdotal. We are aware of one case of cerebellar hemorrhage requiring neurosurgical intervention in a VHL patient receiving the experimental VEGFR tyrosine kinase inhibitor (PTK787, Dr. Dan George, Duke University, Personal Communication). Gingival bleeding as well as one case each of hemoptysis and cerebellar hemorrhage has been described in studies with ZD6474, although it is unclear whether these events are attributable to the agent. A risk of serious bleeding events cannot be excluded in patients receiving this drug.

### **1.2.6 Rationale**

Localized clear cell renal carcinoma in VHL patients requires surgical therapy, which often needs to be repeated multiple times. The surgical therapy is not curative, but is recommended in order to decrease the likelihood of metastasis. Once metastasis has occurred, clear cell renal cancer is incurable in the majority of VHL patients with currently available therapies.

Insight into the molecular pathways believed to mediate the VHL phenotype has provided the impetus for the development of rational targeted therapeutic strategies directed against this condition. Inactivation of the *VHL* gene, the underlying molecular defect in VHL, results in decreased ubiquitin-dependent degradation of hypoxia-inducible factors (HIFs), which in turn leads to overexpression of VEGF as well as other genes such as transforming growth factor- $\beta$  (TGF- $\beta$ ), platelet derived growth factor (PDGF) and GLUT-1. Overexpression of VEGF is responsible for enhanced tumor angiogenesis and leads to the highly vascular renal tumors seen in VHL patients. ZD6474 inhibits angiogenesis by inactivation of the tyrosine kinase activity of the VEGF receptor KDR/VEGFR2. In addition, ZD6474 may exert direct antitumor activity via its inhibition of EGF-R, one of the ligands for which is TGF- $\beta$ . ZD6474 has shown activity in several preclinical tumor models and has demonstrated an acceptable toxicity profile in phase I and phase II studies. ZD6474 thus provides an exciting opportunity for exploring a targeted approach in a hereditary syndrome with a well characterized molecular defect and no available curative options.

## **2 ELIGIBILITY ASSESSMENT AND ENROLLMENT**

### **2.1 ELIGIBILITY CRITERIA**

#### **2.1.1 Inclusion Criteria**

- Patients must satisfy all the following criteria to be eligible for study enrolment



- Clinical diagnosis of von Hippel Lindau disease ([Appendix E](#))
- The presence of at least one measurable (as defined by RECIST) renal tumor (RCC). Patients with tumors localized to the kidney as well as those with metastatic RCC are eligible.
- Age  $\geq$  18 years.
- Life expectancy  $>3$  months
- Performance status ECOG 0-2
- Patients must have normal organ and marrow function as defined below: WBC count  $\geq 3,000/\mu\text{L}$ , absolute neutrophil count  $\geq 1,500/\mu\text{L}$ , platelet count  $\geq 100,000/\mu\text{L}$ , serum creatinine  $\leq 1.5$  times upper limit of reference range or measured 24 hr. creatinine clearance  $\geq 50$  ml/min, AST and ALT  $<2.5$  x upper limit of reference range, total bilirubin  $< 1.5$ x upper limit of reference range (  $<3$  x upper limit of reference range in patients with Gilbert's disease), alkaline phosphatase  $\leq 2.5$  x upper limit of reference range (or  $\leq 5$  x upper limit of reference range if considered to be related to liver metastases by the PI)
- No history of serious intercurrent medical illness
- At least four weeks from completion of any other surgical or investigational therapy for von Hippel Lindau and at least 4 weeks from any major surgical procedure. In addition, patients who have undergone recent major surgery should have well healed surgical incisions.
- All men and women of childbearing potential must use effective contraception
- Negative pregnancy test in female patients of childbearing potential within 7 days prior to enrolment on study
- Ability to understand and the willingness to sign a written informed consent document.

### 2.1.2 Exclusion Criteria

- Prior or concomitant non-von Hippel Lindau associated malignancy with the exception of adequately treated basal or squamous cell carcinoma of the skin, cervical carcinoma in situ or any other malignancy from which the patient has remained disease free for more than five years
- Known brain metastases (unless adequately resected or irradiated with no evidence of recurrence for at least 6 months)
- Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events (to  $\leq$  grade 1 CTCAE v3.0) due to agents administered more than 4 weeks earlier.
- Patients may not be receiving any other investigational agents or have received treatment with a non-approved or investigational drug within 4 weeks prior to Day 1 of study treatment except those used for imaging studies. Use of 5HT-3 antagonists because of the potential effect on QTc interval
- Any concurrent medication that may cause QTc prolongation or induce Torsades de Pointes ([Appendix C](#)). Drugs listed in [Appendix C](#), Table 2, that in the investigator's opinion cannot be discontinued, are allowed however, must be monitored closely.
- Concomitant medications that are potent inducers of CYP3A4 function, such as rifampin, rifabutin, phenytoin, carbamazepine, barbiturates such as phenobarbital, or

St. John's Wort (See [Appendix D](#)).

- Clinically significant cardiac event (including symptomatic heart failure, myocardial infarction or angina) within 3 months of entry or presence of any cardiac disease that in the opinion of the Principal Investigator increases the risk of ventricular arrhythmia
- History of clinically significant arrhythmia [including multifocal premature ventricular contraction (PVC), bigeminy, trigeminy, ventricular tachycardia] that is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia
- Uncontrolled atrial fibrillation. Atrial fibrillation controlled on medication is not excluded.
- Presence of Left bundle branch block
- Previous history of QTc prolongation while taking other medications that required discontinuation of that medication.
- Congenital long QT syndrome or first degree relative with unexplained sudden death under the age of 40 years
- QTc with Bazett's correction that is unmeasurable, or  $\geq 480$  msec on screening ECG. If a patient has QTc  $\geq 480$  msec on screening ECG, the screen ECG may be repeated twice (at least 24 hours apart). The average QTc from the three screening ECGs must be  $< 480$  msec in order for the patient to be eligible for the study). Patients who are receiving a drug that has a risk of QTc prolongation (see [Appendix C](#), Group/Table 2) are excluded if QTc is  $\geq 460$  msec.
- Potassium concentration less than 4.0 mEq/L, calcium (ionized calcium or adjusted for albumin), or magnesium concentrations outside normal limits despite optimal supplementation/correction
- Left ventricular ejection fraction less than 45% measured by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO)
- Hypertension not controlled by medical therapy (systolic blood pressure greater than 150 mmHg or diastolic blood pressure greater than 100 mmHg).
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patient known to be HIV positive and requiring antiretroviral therapy
- Currently active diarrhea that may affect the ability of the patient to absorb ZD6474 or tolerate further diarrhea.
- Patients on therapeutic anticoagulation
- Patients with known bleeding disorders
- Pregnant women are excluded from this study because ZD6474 is an anti-angiogenic agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ZD6474, breastfeeding should be discontinued if the mother is treated with ZD6474
- Any known hypersensitivity to ZD 6474 or other excipients of ZD6474

### **2.1.3 Restrictions**

- Patients who are blood donors should not donate blood during the trial and for 3 months following their last dose of trial treatment.
- Due to the experimental nature of ZD6474, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception during and continued after the last dose of study med (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation.) Male patients must be surgically sterile or using an acceptable method of contraception during their participation in this study. Contraceptive use will continue for at least two months, five half-lives, after the last dose of study medication.
- Both men and women and members of all races and ethnic groups are eligible for this trial.

## **2.2 RESEARCH ELIGIBILITY EVALUATION**

### **2.2.1 History and Physical**

Complete history and physical examination and assessment of performance status will be obtained at the first clinic visit (screening visit) followed by interim assessments at each visit. The H&P and performance status need only be recorded upon the initial assessment and where pertinent changes (improvement or deterioration of previously abnormal findings, new findings or a change in performance status) are noted. Patients will be asked to keep a diary of their side effects, time of occurrence, and medications or interventions for relief. This will be reviewed with the team at each visit.

### **2.2.2 The following must be performed within 4 weeks of enrollment on study**

- Imaging studies: PA and lateral chest X-ray, CT of the chest, abdomen and pelvis (or MRI scans when indicated)
- MRI of brain to include: pre-contrast T-1 and T-2 weighted images in the axial plane and post-contrast (Gadolinium) T-1 weighted images in the axial, sagittal or coronal planes (1 hour scan time). CT imaging with and without contrast may be performed if MRI cannot be performed.
- ECHO
- 12 lead EKG

### **2.2.3 The following must be performed within 7 days of enrollment on study**

#### **History and physical - Limited interim evaluation focusing on significant changes or deviations from initial H&P**

CBC with differential, Chem 20 panel, urinalysis

Urine or serum pregnancy test in women of childbearing potential.

## **2.3 REGISTRATION PROCEDURES**

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site

(<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>)

must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call the pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. *Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information.* A recorder is available during non-working hours. The Central Registration Office will be notified when a patient is withdrawn from the study.

### **3 STUDY IMPLEMENTATION**

#### **3.1 STUDY DESIGN**

This is a phase II study utilizing a fixed dose of ZD6474 (300mg/day PO). The study will recruit patients with von Hippel Lindau disease who have at least one measurable renal tumor (either localized to the kidneys and/or metastatic). Based on phase I evaluation, 300mg/day was identified as a well tolerated dose and appears to result in serum concentrations of the drug compatible with inhibition of target receptor tyrosine kinases. Treatment cycles will consist of 28 days and the drug will be administered daily on days 1-28. There will be no break between 2 consecutive cycles (i.e, drug administration will be continuous). Patients will undergo clinical and laboratory evaluation in the Urologic Oncology Branch clinic prior to the start of each cycle. Patients will be evaluated radiologically for evidence of response or progression approximately twelve weeks after initiation of therapy and every twelve weeks thereafter while on study. Patients with evidence of stable disease or disease response in renal tumors (CR or PR) will continue to receive therapy in the absence of serious toxicity. Patients who demonstrate disease progression at any time will be taken off study. Patients who continue to demonstrate at least one tumor >3cm following 12 weeks or more of therapy may be taken off study regardless of response status, if, in the opinion of the PI, this lesion(s) poses a significant risk of metastasis in the absence of surgical intervention or could otherwise compromise patient care. These patients will be evaluable for the primary end-point (disease response).

Non-renal VHL associated lesions are usually followed until they reach a certain size or become symptomatic, at which point surgical resection or other treatments (such as laser photocoagulation of retinal angiomas) of these lesions is pursued. It is also conceivable, although unlikely, that patients with pheochromocytomas or pancreatic neuroendocrine tumors may develop metastatic disease that may necessitate chemotherapy. Patients with progression of non-renal lesions requiring systemic antineoplastic therapy or surgical intervention will discontinue study drug even in the absence of renal progression or unacceptable toxicity. Vandetanib may be restarted in patients undergoing resection of non-renal VHL lesions once the surgical incisions have adequately healed, if in the opinion of the PI, this is likely to offer clinical benefit (e.g. patients demonstrating an ongoing response in their renal tumors while on vandetanib). Patients with progression of non-renal lesions not requiring intervention but demonstrating stable or responding renal lesions will continue ZD6474 at the discretion of the PI/Study Chair.

## **3.2 STUDY DRUG ADMINISTRATION**

### **ZD6474 Administration**

Treatment will be self-administered by the patient on an outpatient basis. The starting dose of ZD6474 is 300mg/day administered PO daily. Patients with moderate renal failure defined as creatinine clearance  $>$  than or  $=$  30ml/min and  $<$ 50ml/min should begin vandetanib at a reduced dose of 200mg. ZD6474 should be taken with some food and water to minimize GI effects, ideally at around the same time every morning. ZD6474 is available as 50mg, 100mg, 200mg and 300mg tablets and as an oral solution (15 mL of 10mg/mL vandetanib in 25 mg oral solution bottles). Patient compliance will be tracked using a pill count/administration form which the patient will be instructed to complete and which will be reviewed at each clinic visit. If the subject inadvertently does not take the dose in the morning, he or she may take that day's dose any time up to 10pm that same day. However, if a subject misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose and the missed dose will not be made up.

Reported adverse events and potential risks are described in Section 8. Appropriate dose modifications for ZD6474 are described in Section 3.3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

## **3.3 DOSING DELAYS/DOSE MODIFICATIONS**

Patients will be asked to record side effects/symptoms developing or worsening on therapy on a Side Effect Diary which will be reviewed by the research nurse/PI/associate investigator during clinic visits. Treatment modifications will be made in the event of toxicities (graded based on NCI Common Toxicity Criteria for Adverse Events, version 3.0) according to the guidelines below, with dose levels as defined below:

- Dose level 0: 300mg/day
- Dose level -1: 200mg/day
- Dose level -2: 100mg/day
- Dose level -3: 100mg every other day

### **3.3.1 Management of Skin Toxicity**

Patients will be instructed to follow a program of sun protective measures while receiving study therapy and for 3-4 weeks after discontinuing study therapy. These measures include minimizing sun-exposure, using protective clothing, hats etc., and the use of sunscreens. The aim is to reduce the risk of development of skin rash, minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy.

If a patient develops a skin rash,  
The rash should be graded/assessed by a physician as soon as possible according to the CTCAE cutaneous toxicity criteria and documented accordingly

If a rash of CTCAE grade 2 or higher is detected, symptomatic treatment should be provided.



A variety of agents can be used to manage skin rashes and associated symptoms. These include mild to moderate strength steroid creams or oral corticosteroids, topical or systemic antibiotics, topical or systemic antihistamines, emollients and occasionally retinoid creams.

If a rash of CTCAE grade 3 is detected, ZD6474 should be withheld until recovery to grade 1 or below, at which point, the drug may be restarted at one dose level lower

Patients with CTCAE grade 4 rash will discontinue therapy and will not be retreated.

If grade 3 higher cutaneous toxicity recurs at reduced dose of ZD6474, the patient will permanently discontinue study treatment of ZD6474. If ZD6474 must be withheld for >3 weeks due to cutaneous toxicity, the patient will be taken off study.

### **3.3.2 Management of gastrointestinal (GI) toxicity**

If GI toxicity is not appropriately managed this may be associated with a development of dehydration. Electrolytes should be monitored in the event of persistent vomiting or diarrhea.

#### **3.3.2.1 Nausea and/or vomiting**

In subjects who have emesis and are unable to retain study treatment, every attempt should be made to obtain control of nausea and vomiting. The dose of study treatment may be repeated if emesis occurs within 30 minutes of taking the tablets or all the tablets are seen in the emesis.

Nausea, vomiting, or both may be controlled with antiemetic therapy; however, 5HT-3 antagonists are not permitted because of the potential effect on QTc interval.

#### **3.3.2.2 Diarrhea**

Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Diarrhea related to ZD6474 has been successfully managed with anti-diarrheal agents such as loperamide. Once diarrhea is determined to be related to ZD6474, an acceptable strategy for symptomatic management is initiation of loperamide 2mg po administered following the first episode, which can be repeated as frequently as every 2 hours while awake (or administered at a dose of 4mg every 4 hours during sleeping hours) (not to exceed a total of 16mg/24 hours) until the patient is diarrhea-free for 8-12 hours.

No dose modifications will be made for CTCAE grade 1 or 2 nausea, vomiting or diarrhea. If CTCAE grade 3 nausea, vomiting, or diarrhea develops despite optimal pharmacologic prophylaxis/treatment, study medication should be withheld until symptoms resolve to less than or equal to grade 1. Once the diarrhea resolves to less than or equal to grade 1, treatment with ZD6474 may recommence with a dose reduction of one level. If the toxicity reoccurs on the dose reduction pack, the subject will be withdrawn from the study. Subjects who develop grade 4 nausea, vomiting, or diarrhea will discontinue therapy with ZD6474. Subjects who are clinically unstable because of nausea, vomiting, diarrhea or other intercurrent medical illness must be admitted and evaluated using telemetry until clinically stable.

### **3.3.3 QT prolongation**

QT prolongation will be managed as follows:

### **Monitoring for QT prolongation**

All patients on study will get a weekly 12 lead EKG for the first 2 cycles. Thereafter (in the absence of QT prolongation), a monthly ECG will be performed while the patient is on the study drug. The following algorithm will be used to monitor/manage QTc prolongation.

### **QTc prolongation is defined as**

A single QTc value of  $\geq 500$  msec or an increase of  $\geq 100$  msec from baseline;

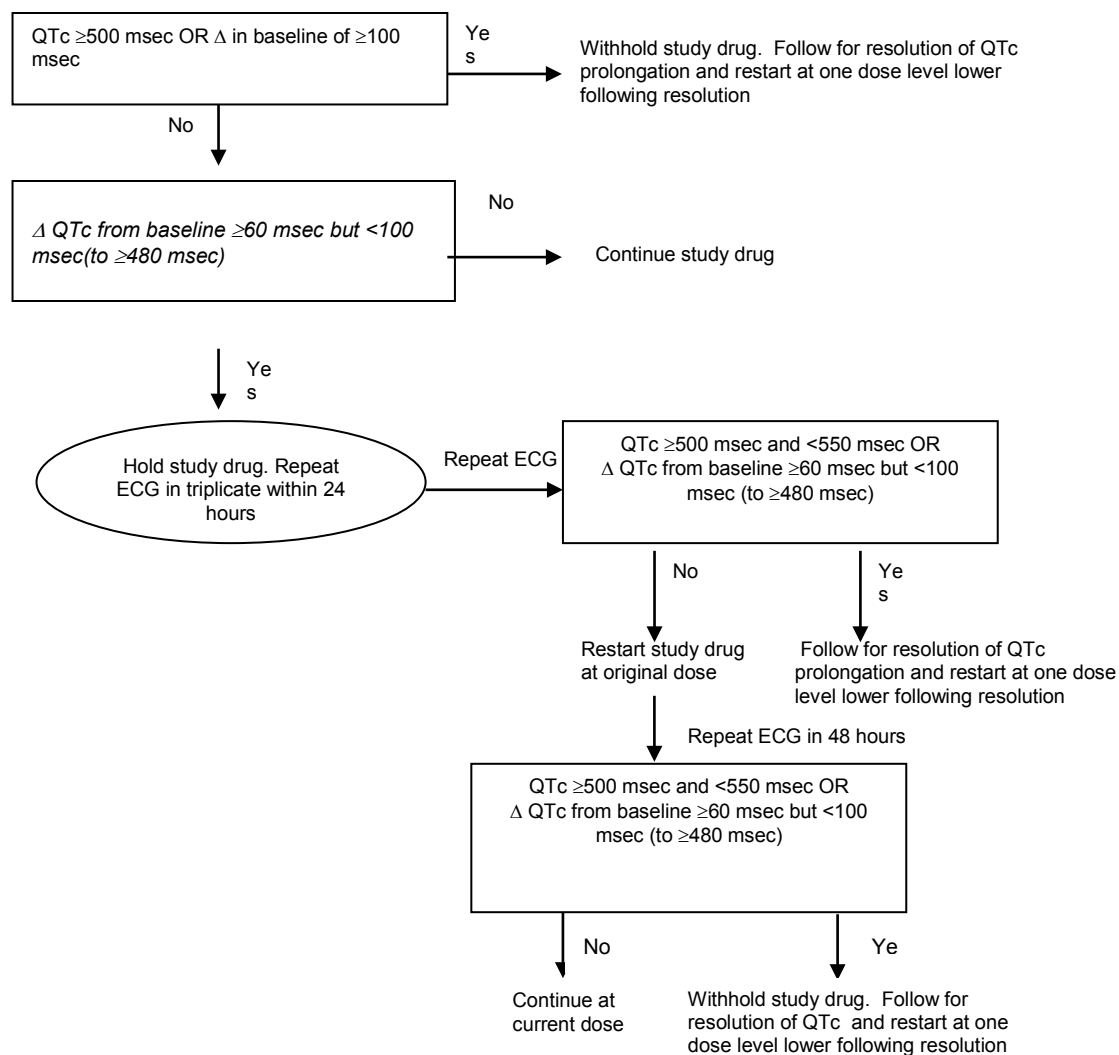
### **OR**

Two QTc measurements where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):

A QTc interval  $\geq 500$  msec but  $< 550$  msec, **OR**  
An increase of  $\geq 60$  msec, but  $< 100$  msec, from baseline QTc to a QTc value  $\geq 480$  msec.  
Management of Patients With QTc Prolongation

For a single QTc value of  $\geq 500$  msec or an increase of  $\geq 100$  msec from baseline, ZD6474 must be withheld. ECGs and electrolytes should be followed 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. ZD6474 treatment may be resumed at a lower dose after the QTc recovers to  $< 480$  msec or baseline.

For a QTc  $\geq 500$ ms but  $< 550$ ms (grade 3 CTCAE v3.0) or  $\geq 60$ ms, but  $< 100$ ms compared to baseline to a QTc value  $\geq 480$  msec, further ZD6474 dosing will be withheld and an ECG (in triplicate) obtained within 24 hours. If the repeat ECGs confirm a QTc  $\geq 500$  (mean calculated from 3 ECGs) or prolongation of  $\geq 60$ ms from baseline to a QTc  $\geq 480$ ms, QTc and electrolytes will be monitored three times a week until the QTc returns to baseline or below 480ms (whichever is higher); thereafter, ZD 6474 will be resumed at one lower dose level. If the repeat ECG reveals a QTc  $< 500$  ms or a prolongation of  $< 60$ ms from baseline, ZD6474 will be resumed at the current dose and an ECG repeated in 48 hours and thereafter as outlined in the study plan in the absence of QT prolongation (i.e,  $\geq 500$ ms or prolongation  $\geq 60$ ms from baseline to a value  $\geq 480$  msec). A second instance of QTc  $\geq 500$ ms (but  $< 550$ ms) or QTc prolongation  $\geq 60$ ms from baseline to a value  $\geq 480$  msec will necessitate withholding drug until normalization of QTc and resumption thereafter at one lower dose level.



### 3.3.4 Hypertension

Subjects will be asked to monitor their blood pressure at home at least once a day and contact the UOB team for elevated readings. However, elevated BP readings should be confirmed by a qualified health care professional and decisions regarding grading of hypertension and initiation/intensification of antihypertensive therapy will be driven by BP measurements performed by a health care professional. Table 1 outlines the management plan for patients developing hypertension on therapy. Although CTCAE criteria will be used to grade hypertension, the scheme outlined in Table 1 will be used to guide dose modifications. Early treatment of grades 1-2 hypertension to prevent or minimize the risk of developing more persistent or clinically significant hypertension is allowed and is not considered a grade 3 event.

Agents typically used to treat hypertension include calcium channel blockers such as amlodipine (agents such as verapamil or diltiazem, which are potent inhibitors of CYP3A4 should be avoided where possible, as should agents in this category that have the potential to prolong QTc), diuretics, ACE inhibitor, beta-blockers and angiotensin receptor antagonists. The choice of agents and dosage used may vary based on individual circumstances.

**Table 1**

	<b>BP Measurements - Systolic/Diastolic</b>	<b>Treatment/Dose Modification</b>
A	>150 mmHg (systolic) OR >100 mmHg (diastolic) OR Increase of diastolic BP by $\geq 20$ mmHg regardless of baseline BP	<ul style="list-style-type: none"> <li>• Add new or additional antihypertensive medications or increase dose of existing medications.</li> <li>• Maintain dose of ZD6474.</li> <li>• If unable to control BP to &lt;150/100 in two weeks, hold ZD6474 and follow guidelines under row C</li> </ul>
B	>180 mmHg (systolic) OR >110 mmHg (diastolic) OR Symptomatic	<ul style="list-style-type: none"> <li>• Hold ZD6474.</li> <li>• Add new or additional antihypertensive medications or increase dose of existing medications.</li> <li>• Resume treatment at same dose level when BP falls to &lt;140/90 or baseline.</li> </ul>
C	>150 mmHg (systolic) OR >100 mmHg (diastolic) Despite therapy for at least 2 weeks	<ul style="list-style-type: none"> <li>• Hold ZD6474.</li> <li>• Maintain or intensify antihypertensive therapy</li> <li>• Resume treatment at one lower dose level when BP falls to &lt;140/90 or baseline</li> </ul>
D	CTCAE Grade 4	<ul style="list-style-type: none"> <li>• Discontinue ZD647</li> <li>• No further treatment with ZD 6474 allowed except in patients benefiting from therapy in whom ZD6474 may be restarted at one lower dose level if BP is controlled to &lt;140/90 within 3 weeks and there are no permanent sequelae. Patient will be removed from study if a second episode of grade 4 hypertension occurs</li> </ul>

### 3.3.5 Other Toxicity

If any other CTCAE grade 3 or 4 non hematologic toxicity attributable to ZD6474 develops (not outlined in Section 3.3.1-3.3.4), study treatment should be interrupted until the toxicity resolves to less than or equal to CTCAE grade 1 or baseline. At the time of resolution, patients with grade 3 toxicity may resume study treatment at one dose level lower. Patients with grade 4 nonhematologic toxicity will discontinue ZD6474 and be taken off study. Patients with grade 3 or 4 neutropenia or thrombocytopenia attributable to ZD6474 will have their therapy interrupted until resolution to less than or equal to CTCAE grade 1 or baseline, at which point treatment may be resumed at one dose level lower. If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the subject's participation in the study will be discontinued. Dose reductions or study drug interruptions will not be made for laboratory abnormalities not considered clinically significant, regardless of grade.

### 3.4 RESEARCH STUDIES

#### Sample acquisition and planned studies

Blood samples for evaluation of basal plasma levels of angiogenesis biomarkers such as VEGF and to assess the effect of ZD6474 on these biomarkers will be obtained on study entry and at each clinic visit. 5-10 cc of venous blood will be collected into lavender top EDTA tubes and thoroughly mixed.

Peripheral blood (four CPT tubes containing sodium citrate) will be obtained pre-treatment and post-treatment with ZD6474 and coded samples will be used for analysis of angiogenesis markers such as circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEP). The time points may vary as the optimal time vis a vis treatment needs to be empirically determined. Four CPT tubes containing sodium citrate (blue-black speckled top tubes) of peripheral blood will be sent to Jane Trepels's laboratory in the Medical Oncology Branch, CCR, NCI. The CEC and CEP analysis will be performed using multiparameter flow cytometry, and may include ancillary studies such as real-time RT-PCR analysis of gene expression and *in vitro* endothelial cell culture. These studies are exploratory and intended to evaluate the utility of CECs and CEPs as surrogates for inhibition of angiogenesis following administration of ZD6474.

Although there is no universally accepted surrogate for angiogenesis inhibition, evaluation of CECs and CEPs have been proposed and validated by several groups (41-46). Dr. Jane Trepel's lab has collaborated with other groups (Dr. John Heymach, MD Anderson Cancer Center, and the Angiogenesis Core at the Beth Israel and Deaconess Medical Center) to standardize flow cytometric analyses of peripheral blood for evaluation of CEC/CEP. For this analysis, peripheral blood is drawn into 4 CPT citrate tubes. Mononuclear cells are isolated by centrifugation, washed with PBS, and FcR solution (Miltenyi) is added to block non-specific binding. Although the antibodies and fluorochromes used may vary, for identification of CECs and CEPs, cells are typically stained with FITC- conjugated anti-CD31, PerCP-conjugated anti-CD45, APC-conjugated anti-CD133, Hoechst 33258 and PE-conjugated CD146 and analysed on an LSR II flow cytometer (BD Biosciences), using LSR II-equipped digital data acquisition and FlowJo cytometric data analysis software. The CEC and CEP cell concentrations are calculated as a percentage of the total number of mononuclear cells or as the number of cells/microliter of whole blood after an evaluation of a minimum of  $10^5$  cellular events, and preferably  $10^6$  cellular events. CEC cells are defined by the co-expression, or absence of expression on a single cell of the following parameters: CD45-, CD31+, CD133- and CD146+, Hoechst 33258 (viable CEC) or CD45-, CD31+, CD133- and CD146+, Hoechst 33258+ (nonviable CEC). CEP cells are defined by the co-expression, or absence of expression on a single cell of the following parameters: CD45- or dim, CD31+, CD133+ and CD146-, Hoechst 33258- (viable CEP) or CD45- or dim, CD31+, CD133+ and CD146-, Hoechst 33258+ (nonviable CEP).

The outcome measures will be the number of CEC and CEP per  $10^6$  mononuclear cells or per microliter of peripheral blood, analyzed in samples taken before and after treatment. These numbers will then be examined for correlations with various parameters to assess their potential utility as surrogate biomarkers for drug activity, for establishing the optimal biologic dose, for patient stratification, and monitoring of therapy-related side effects.

In addition to multi-parameter flow CEC and CEP analysis, if there are a sufficient number of cells in the mononuclear fraction the cells will be set up *in vitro*, according to standard methods, for the endothelial progenitor cell colony forming assay (47, 48).

Correlative laboratory studies will be performed by investigators in the Urologic Oncology Branch and may involve collaboration with other NIH intramural investigators and/or Astra-Zeneca. Studies listed will be performed wherever possible and as permitted by sample and resource availability.

### **3.4.1 Collection, Storage, Use and Disposition of Human Specimens**

#### **3.4.1.1 Clinical Samples**

Blood and urine samples for clinically relevant, non-research hematology, serum chemistry, urinalysis, and skin biopsy tissue will be prepared using standard procedures. Routine clinical analyses will be performed by the NIH Clinical Center central laboratories or NCI Pathology department. Samples will be processed and disposed according to standard laboratory procedure.

#### **3.4.1.2 Storage and research use of research human specimens**

- a) Sample Collection and Planned Research Studies-Research samples will be collected with a view to performing a variety of correlative/biomarker studies (as indicated in section 3.4).
- b) Sample Processing and Storage-Each patient research sample will be assigned a unique patient identifier and relevant sample characteristics (such as timing of sample collection, treatment cycle and day identifiers) will be recorded. The location of all samples will be carefully tracked in the database. All stored samples will be coded and no identifying patient information will be on placed on sample containers. Stored samples will be kept in freezers / refrigerators or secure containers located in the Urologic Oncology Branch research laboratories.
- c) Time frame for research studies- Samples will be stored until requested by an authorized researcher(s). All researchers are required to use the samples for research purposes associated with this trial (as per the NCI IRB approved protocol). Subjects will be given the option of consenting to future use of their research samples per the informed consent process with their option declared in the consent document. Samples from those patients who consent to this will be stored permanently. However, these samples will be used only for research studies on active NCI IRB approved protocols covered by a valid informed consent document. Samples will be destroyed at the completion of the study from those subjects who decline future use of their samples. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent. Any unused samples must be returned to the UOB laboratories as appropriate. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (e.g. broken freezer or lack of dry ice in a shipping container) or if samples are destroyed because a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Any freezer problems, lost

samples or other problems associated with samples will be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

### **3.5 STUDY EVALUATIONS AND SCHEDULE**

#### **3.5.1 Baseline Evaluation**

These studies are intended to evaluate the presence and extent of nonrenal VHL-associated tumors and are not meant to determine eligibility. These studies may be performed before (as part of routine evaluation of VHL patients) or after eligibility assessment but no more than 3 months prior to study enrolment.

3.5.1.1 MRI of the spine to include: precontrast T-2 weighted surface coil images of the cervical and thoracic cord in the sagittal plane and post contrast (Gadolinium). CT imaging with and without contrast may be performed if MRI cannot be performed.

3.5.1.2 24 hour urine collection for catecholamine analysis when clinically indicated.

3.5.1.3 Standard complete audiogram to detect hearing loss and /or the presence of an ELST (endolymphatic sac tumor) in patients known or suspected to have these tumors.

3.5.1.4 CT examination of the internal auditory canal to evaluate for potential ELST in patients known or suspected to have these tumors.

3.5.1.5 For males, ultrasound of testicles with high resolution (5-7 MHz) transducer to evaluate the epididymis (0.75 hour scan time) when clinically indicated.

3.5.1.6 An ophthalmologic exam to screen for retinal angiomas.

3.5.1.7 Labs: serum erythropoietin, TSH, T3 and FreeT4, parathyroid function tests –spot urine phosphorous and spot urine creatinine, vitamin D 1-25, vitamin D 25-OH Serum PTH, FGF23 (1-2ml of plasma to be sent to Michael T. Collins, M.D., Chief, Skeletal Clinical Studies Unit, CSDB, NIDCR)

#### **3.5.2 On Study Evaluation**

3.5.2.1 Before every cycle: Based on patient's status and schedule conflicts if deemed warranted pt's may be allowed to reschedule NIH protocol visits at the discretion of the PI, the patient and the research team.

- a. History and physical
- b. CBC, Chem 20, urinalysis and urine protein:creatinine ratio.
- c. ECG (A 12-lead ECG should be obtained on day 1, cycle 1 before the first dose of ZD6474 and repeated 4-8 hours after the first dose)
- d. Urine pregnancy test in women of childbearing potential

3.5.2.2 Every three cycles (Restaging cycles): Based on patient's status and schedule conflicts if deemed warranted pt's may be allowed to reschedule NIH protocol visits at the discretion of the PI, the patient and the research team.

- e. History and physical
- f. CBC, Chem 20
- g. Erythropoietin
- h. TSH, if elevated, T3 and Free T4, antiTPO and TSI and lipid panel
- i. Parathyroid function tests – serum PTH, spot urine phosphorus, spot urine creatinine, vitamin D 1-25, vitamin D 25-OH and FGF23 (1-2ml of plasma to be sent to Michael T. Collins, M.D., Chief, Skeletal Clinical Studies Unit, CSDB, NIDCR)
- j. ECG
- k. Imaging studies: CT/MRI/Ultrasound evaluation of known/suspected disease sites (both renal and non-renal VHL associated lesions)
- l. Ophthalmologic evaluation in patients with baseline retinal angiomas
- m. Serum and Urine catecholamines in patients with baseline elevations

#### 3.5.2.3 Weekly Monitoring

- n. 12 lead ECG for the first two cycles (within 4-8 hours after dose)
- o. Chem 20 for the first two cycles

#### 3.5.2.4 Daily Monitoring

Blood Pressure- Patient will be asked to measure and record his blood pressure at least once a day and will be provided with a BP monitor. Patients will be instructed to record BP readings on a BP monitoring diary which will be provided and will be reviewed by the research nurse/PI/AI at each clinic visit. In addition, patients will call the UOB research team for readings above 150/100mm Hg and may be instructed to have elevated readings confirmed by a local health care provider.



### 3.6 STUDY CALENDAR

Cycle	Screening	1				2				3	4	Daily	Every Cycle	Every 3 cycles (Cycle 4 onwards)	Disease Progression/ Withdrawal from study
Day (D) of Cycle (+/- 3 days)		1	8	15	22	1	8	15	22	1	1				
Weeks		1	2	3	4	5	6	7	8	9	13				
Visit	1	2		3		4				5	6				
Informed consent	X														
Medical history	X														
Eligibility Evaluation	X														
History & Physical examination	X <sup>a</sup>	X		X		X				X	X		X		X
ECHO	X														
Vital signs/ weight	X <sup>a</sup>	X		X		X				X	X		X		X
BP Monitoring												X			
12-lead ECG	X <sup>b</sup>	X <sup>c</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sub>d</sub>	X <sub>d</sub>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>		X <sup>d</sup>		X
(Chem 20)/ (CBC)	X <sup>a</sup>	X				X				X	X		X		X
Chem 20			X	X	X		X	X	X						
Thyroid and parathyroid function tests	X													X	
Urinalysis	X <sup>a</sup>					X				X	X		X		
Pregnancy test	X <sup>a</sup>												X		
ECOG performance status	X <sup>a</sup>					X				X	X		X		X
RECIST Assessment	X <sup>b</sup>										X			X	
Dispense ZD6474		X				X				X	X		X		
Sample for Biomarkers	X <sup>b</sup>			X		X				X	X		X		X
Tolerability/ AE reporting		X		X		X				X	X		X		X
Concurrent treatment	X <sup>b</sup>	X		X		X				X	X		X		X

<sup>a</sup> Should be performed within 7 days prior to enrolment on study, pregnancy test performed only in women of childbearing potential

<sup>b</sup> Should be performed within 4 weeks prior to enrolment on study

<sup>c</sup> A 12-lead ECG should be obtained on day 1, cycle 1 before the first dose of ZD6474 and repeated 4-8 hours after the first dose

<sup>d</sup> Should be performed 4-8 hours after ZD6474 dose

### **3.7 CONCURRENT THERAPIES**

Coadministration of ZD6474 and drugs with potent CYP3A4 inducer effects are not allowed. Agents with potent inhibitory effects on CYP3A4 should be avoided where possible. (Please see [Appendix D](#)) Other agents with some modulation of and/or metabolism through CYP3A4 can be used with caution at the discretion of the Principal Investigator. ZD6474 should also not be administered in patients receiving drugs known to prolong QT interval or induce torsades de point. (Please see [Appendix C](#)). No concurrent systemic anti-neoplastic therapy for VHL-associated tumors will be allowed.

### **3.8 SURGICAL GUIDELINES**

Major elective surgical procedures should not be scheduled during protocol treatment or within 4 weeks of the last dose of drug. Patients undergoing unexpected major surgical procedures should have ZD6474 withheld. Treatment may be resumed at a later date at the discretion of the PI, no earlier than 4 weeks post-operatively, with adequately healed incisions.

### **3.9 OFF STUDY CRITERIA/OFF TREATMENT CRITERIA**

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression per RECIST criteria of targeted renal lesions
- Disease progression of non-renal lesions requiring surgical intervention or systemic anti-neoplastic therapy. Vandetanib may be restarted in patients undergoing resection of non-renal VHL lesions once the surgical incisions have adequately healed, if in the opinion of the PI, this is likely to offer clinical benefit (e.g. patients demonstrating an ongoing response in their renal tumors while on vandetanib).
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) that necessitates discontinuation of ZD6474, including most grade 4 and recurrent grade 3 toxicities (CTCAE v3) as outlined in section 3.3 as well as any other adverse event that renders further treatment unsafe in the opinion of the investigator
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

In the event of a complete radiologic response, treatment will continue for 2 cycles beyond CR. Patients may be retreated at the discretion of the PI in the event of disease recurrence.

### **3.10 POST-TREATMENT FOLLOW-UP**

Patients with unresolved toxicities (to  $\leq$  CTCAE 3.0 grade 1) may be followed to enable monitoring and/or management of these toxicities. Patients may be followed-up by telephone or other means of communication periodically to determine disease status.

## **4 SUPPORTIVE CARE**

Supportive care will be provided in accordance with good medical practice

## **5 DATA COLLECTION AND EVALUATION**

### **5.1 DATA COLLECTION**

Data will be prospectively collected and entered in a designated database (C3D). All radiographic images will be stored in the Dept. of Radiology, Clinical Center, NIH and will be reviewed by a medically responsible investigator and/or a clinical center radiologist.

For the purposes of this study, patients should be reevaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

**End of study procedures:** Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

### **5.2 RESPONSE EVALUATION**

#### **5.2.1 Definitions**

Response and progression of renal tumors will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

##### **5.2.1.1 Measurable disease**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm with conventional techniques (CT, MRI, x-ray) or as  $\geq 10$  mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

##### **5.2.1.2 Non-measurable disease**

All other lesions (or sites of disease), including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

#### 5.2.1.3 Target lesions

All measurable RCC lesions up to a maximum of five lesions per kidney and a total of ten lesions should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

#### 5.2.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. If the lesions are too numerous to list, not all lesions may be listed at the discretion of the investigator and/or radiologist.

### 5.2.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. For each restaging study, lesions will be recorded in the same order as with the baseline study.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

**Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**Chest x-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**Conventional CT and MRI.** These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

**Ultrasound (US).** When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical

measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

**Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

**Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

**Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

### 5.2.3 Response Criteria

#### 5.2.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

#### 5.2.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above

the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

### 5.2.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

## **5.2.4 Confirmatory Measurement/Duration of Response**

### **5.2.4.1 Confirmation**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed  $\geq 4$  weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks

### **5.2.4.2 Duration of overall response**

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured **from** the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

### **5.2.4.3 Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

## **5.2.5 Evaluation of non-renal tumors associated with VHL**

Evaluation of the effect of ZD6474 on non-renal tumors associated with VHL disease is one of the secondary end-points of this study. Since there is significant interpatient variability in the location and number of visceral and non-visceral tumors, each tumor type will be assessed individually. In each individual patient, the presence of one or more of the following tumors at baseline will be documented and response following treatment with ZD6474 will be assessed:

- 1) Pancreatic tumors/cysts
- 2) CNS Hemangioblastomas
- 3) Pheochromocytomas

### **5.2.5.1 Identification and measurement of lesions to be followed, and response criteria will follow the scheme outlined in Sections [5.2.1](#) to [5.2.4](#)**

### **5.2.5.2 Evaluation of retinal angiomas will include the following:**

- a) Measurement of visual acuity
- b) Size-Largest unidimensional measurements will be recorded where appropriate
- c) Visual field evaluation
- d) Fluorescein leakage

Since standard tumor response criteria such as RECIST cannot be applied to ocular lesions, changes in the above parameters will be recorded descriptively.

5.2.5.3 Patients with progressive disease in non-renal lesions which require medical or surgical intervention shall be taken off study for progressive disease. Patients with progressive disease in non-renal lesions not requiring intervention but stable disease or responding disease in renal lesions will be continued on ZD6474 to the discretion of the PI or Study Chair.

### 5.3 TOXICITY CRITERIA

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>)

## 6 STATISTICAL SECTION

This is a phase II study to establish whether treatment of ZD6474 in patients with von Hippel Lindau disease and renal tumors results in an adequate fraction of clinical responses (partial response plus complete response) to warrant further development. The study will be conducted with a Simon two-stage optimal design (Simon R. Controlled Clinical Trials 10:1-10;1989) which allows for an early look for futility. For the purposes of phase II evaluation, clinical response will be defined as either a partial or complete response occurring at any time after initiation of therapy. All responses must be confirmed  $\geq 4$  weeks after the initial response is documented. Twelve patients will be accrued into the first stage. If 1 or more of the 12 patients respond, accrual will proceed to the second stage of the design. Twenty-five additional patients will be accrued in the second stage for a total accrual of 37 patients. If 4 or more of 37 respond, ZD6474 will be considered worthy of further investigation in this population. If fewer than 4 patients of 37 respond, the agent will be considered to have insufficient activity for further investigation. If after the first 12 patients have been accrued to the study, no patient has had a confirmed response, further accrual will be temporarily suspended for up to a year or until at least one response is seen; if no responses are seen within one year of accrual of the twelfth patient, no further patients will be accrued and the study will not proceed to the second stage.

### 6.1 TWO-STAGE DESIGN

The optimal two-stage design is based on the following design parameters. The fraction of clinical responses is 5% if the agent is ineffective ( $P_0=0.05$ ), while a fraction of clinical responses of 20% ( $P_1=0.2$ ) will be considered worthy of further testing. The probability of falsely concluding that the agent is effective when it is truly ineffective is 0.1 (alpha) and the probability of falsely concluding that the agent is ineffective when it is truly effective is 0.1 (beta). Under this design, the probability of stopping accrual early if the proportion of responses is 5% is 54%.

### 6.2 RESPONSE FREQUENCY

The response frequency for non-renal tumors associated with VHL will be estimated as a secondary objective. Other secondary objectives (Section 1.1) include examining the effect of ZD6474 on, (i) plasma biomarkers of angiogenesis such as VEGF, (ii) endothelial progenitor cells and circulating endothelial cells, (iii) time to progression (defined as the time from the start



of treatment to progression as defined by RECIST criteria, with death being treated as a censored event), and (iv) progression free survival (defined as time from initiation of treatment to either progression as defined by RECIST criteria, section 5.2.3.3, or death). The follow-up times for biomarker endpoints are given in Sections 3.4 and 3.5. Analyses will focus on comparing changes in these biomarkers on treatment from the pre-study measurement. Longitudinal changes in continuous biomarkers (eg. plasma VEGF) or imaging outcomes will be analyzed using paired Wilcoxon-ranked sum tests (which compares measurements at a single post-treatment time point with measurements at the pre-treatment time point) as well as with linear mixed models (which incorporates all follow-up times when evaluating change). Evaluation of time to progression and progression free survival will be based on restaging studies performed approximately every 12 weeks and will be summarized using Kaplan-Meier curves. Available pre-treatment data on tumor size and growth rates will be used to determine if parameters such as TTP/stability are affected by treatment both within individual patients and in the entire treatment group.

### **6.3 ACCRUAL CEILING**

The accrual ceiling for this study is 37 patients. With an expected accrual of 10-12 patients per year, we expect to complete the accrual within 3-4 years.

## **7 HUMAN SUBJECTS PROTECTION**

### **7.1 RATIONALE FOR SUBJECT SELECTION**

#### **7.1.1 Research subject selection**

Patients of all races and ethnic origins will be eligible.

#### **7.1.2 Recruitment**

This study will be recruited through internal referral, our physician referral base, and through Cancer Hotline information.

### **7.2 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS**

#### **7.2.1 Potential benefits**

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms, risk of metastasis and/or survival.

#### **7.2.2 Potential risks**

Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described in sections 3 and 8.

The agent used in this trial is investigational. Experience with this agent to date suggests that this agent is associated with an acceptable toxicity profile. However, VHL patients may be at risk for

previously undefined or inadequately characterized complications from this agent owing to their unique clinical circumstances (e.g. potential risk of bleeding from cerebellar or spinal hemangioblastomas, unmasking or exacerbation of hypertension in patients with asymptomatic or occult pheochromocytomas etc.); these issues have been addressed in the consent document and in the appropriate sections of this protocols. The risk of delaying 'standard of care' therapy (resection of renal tumors  $\geq 3\text{cm}$ ) in favor of an experimental therapy is considered to be minimal. The UOB has extensive experience with the management of VHL-associated renal tumors over the past 17 years. These tumors are slow growing tumors and often there is a 3-4 month time period between when surgery is recommended and is carried out. All patients enrolled on trial will be evaluated for a response of renal lesions following three cycles of therapy.

### **7.2.3 Alternative treatments**

Patients will be apprised of other therapeutic options, both experimental and those of standard care (i.e., observation or surgical intervention).

## **7.3 RISK/BENEFIT RELATIONSHIP**

VHL patients with renal cell carcinoma or other tumors are at risk for morbidity and mortality from complications of local tumor growth and/or metastasis. Standard therapy for these patients is restricted to surgical excision, sometimes performed repeatedly. Patients enrolled on this trial may benefit from tumor regression which may delay or obviate the need for surgical intervention. Although the agent used in this trial is experimental, it has been administered safely in prior phase I and phase II trials and the majority of the side effects have been mild to moderate. The mechanism of action of the drug suggests that the drug could potentially render benefit in VHL patients with clear cell renal cancer.

## **7.4 CONSENT AND ASSENT PROCESSES AND DOCUMENTS**

A medically responsible associate investigator or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. A copy of the signed informed consent will be placed in the patient's medical record and the original held in the Protocol Office.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

## **7.5 PATIENT RECORDS AND QUALITY ASSURANCE**

Complete records must be maintained on each patient treated on the protocol. These records will include primary documentation to confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol.

- Toxicity was assessed according to protocol.
- Response was assessed according to protocol.

## **8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN**

### **8.1 DEFINITIONS**

#### **8.1.1 Adverse Events**

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

The development of a new cancer or tumor that is not VHL related should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

#### **8.1.2 Suspected adverse reaction**

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

#### **8.1.3 Unexpected adverse reaction**

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **8.1.4 Serious**

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

### **8.1.5 Serious Adverse Event**

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### **8.1.6 Disability**

A substantial disruption of a person's ability to conduct normal life functions.

### **8.1.7 Life-threatening adverse drug experience**

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

### **8.1.8 Protocol Deviation (NIH Definition)**

Any change, divergence, or departure from the IRB-approved research protocol.

### **8.1.9 Non-compliance (NIH Definition)**

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

### **8.1.10 Unanticipated Problem**

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.1.11 Relatedness of Adverse Event to an Intervention

The best estimate of the PI at the time of reporting of the causal relationship between an experimental intervention and an adverse event; the degree of certainty about causality is graded as follows:

#### Unrelated:

Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

#### Unlikely (must have 2):

Adverse event:

- (1) does not have temporal relationship to intervention,
- (2) could readily have been produced by the subject's clinical state,
- (3) could have been due to environmental or other interventions,
- (4) does not follow known pattern of response to intervention,
- (5) does not reappear or worsen with reintroduction of intervention

#### Possible (must have 2):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state,
- (3) could not readily have been due to environmental or other interventions,
- (4) follows a known pattern of response to intervention

#### Probable (must have 3):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- (3) follows a known pattern of response to intervention,
- (4) disappears or decreases with reduction in dose or cessation of intervention

#### Definite (must have all 4):

Adverse event:

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- (3) follows a known pattern of response to intervention,
- (4) disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

### 8.1.12 Pregnancy

Pregnancy in women of childbearing potential should be excluded before randomization. Should a pregnancy occur, it must be reported in accordance with the procedures described in this section. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

## **8.2 NCI-IRB AND NCI CLINICAL DIRECTOR (CD) REPORTING**

### **8.2.1 NCI-IRB and NCI CD Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths**

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI CD:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

### **8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review**

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
  - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
  - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
  - All Grade 5 events regardless of attribution;
  - All Serious Events regardless of attribution.

**NOTE:** Grade 1 events are not required to be reported.

### **8.2.3 NCI-IRB Reporting of IND Safety Reports**

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

## **8.3 FDA REPORTING CRITERIA**

### **8.3.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)**

The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug

- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendar days after receiving the request.

### **8.3.2 FDA Annual Reports (Refer to 21 CFR 312.33)**

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

### **8.3.3 Astra-Zeneca Requirements for Reporting AE**

Investigators and other site personnel must inform the FDA, via a MedWatch form, of any serious or unexpected adverse event that occurs in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

A cover page should accompany the MedWatch form indicating the following:

- ZD6474 Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name and AstraZeneca Reference number

#### **Send by way of fax to:**

(302) 886-1528,  
Attention ZACTIMA ISS Safety Representative

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

## **8.4 DATA AND SAFETY MONITORING PLAN**

### **8.4.1 Principal Investigator/Research Team**

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### **8.4.2 Sponsor Monitoring Plan**

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least biannually, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

## **9 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)**

The agent (ZD6474), supplied by Astra-Zeneca, Inc, used in this protocol is provided to the NCI under a Collaborative Research And Development Agreement (CRADA) between tAstra-Zeneca, Inc) [hereinafter referred to as Collaborator(s)] and W. Marston Linehan, M.D., Chief, UOB, CCR, NCI. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing



investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from <http://ctep.cancer.gov>.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data").:
  - a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.
3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

## **10 PHARMACEUTICAL INFORMATION**

### **10.1 SOURCE**

#### **ZD6474 (Vandetanib)**

**Chemical Name and Identification** N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine

Molecular Formula C<sub>22</sub>H<sub>24</sub>BrFN<sub>4</sub>O<sub>2</sub>

Molecular Weight     475.36

## **10.2 SOLUBILITY**

ZD6474 exhibits pH dependent solubility and is relatively insoluble in water with a value of 0.025mg/ml at 25 C

## **10.3 MODE OF ACTION**

Tyrosine kinase inhibitor with specific activity against KDR (IC<sub>50</sub>=40nM) and EGFR (IC<sub>50</sub>=500nM)

## **10.4 FORMULATION AND PREPARATION**

The drug product consists of 3 ranges of white film-coated tablets packed in high density polyethylene (HDPE) bottles and an oral solution presented in Type 1 glass bottles. The first tablet range consisted of a series of tablets containing 25 mg, 100 mg and 200 mg of vandetanib drug substance (25 and 100 mg matched, 200 mg size differentiated) and were used in Phase I studies. The second range is a matched series containing 100 mg, 200 mg, 300 mg and 400 mg tablets. The third range is size differentiated and consists of 50 mg, 100 mg, 200 mg and 300 mg tablets. The oral solution is presented in 25ml bottles containing 15 ml of vandetanib (10mg/ml).

The bottles are sealed with ethylene tetrafluoroethylene (ETFE) copolymer coated chlorobutyl stoppers secured with screw on caps. Each bottle is intended for single use only.

## **10.5 COMPOSITION**

The initial 25 mg, 100 mg and 200 mg tablets contain vandetanib, lactose, povidone, croscarmellose sodium, sodium lauryl sulphate and magnesium stearate with a film coating containing methylhydroxypropylcellulose, polyethylene glycol 300 and titanium dioxide.

The matched second range of tablets (100, 200, 300 and 400 mg) contain vandetanib, calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycollate, povidone, sodium lauryl sulphate and magnesium stearate with a film coating containing methylhydroxypropylcellulose, polyethylene glycol 300 and titanium dioxide. A placebo to match the second range is presented, in which the drug substance is replaced by an appropriate amount of calcium hydrogen phosphate and microcrystalline cellulose.

The non-matched third range of tablets (50, 100, 200 and 300 mg) was developed from the second range. The compositions are the same with the exception that the sodium starch glycollate is replaced with crospovidone and the sodium lauryl sulphate is removed. A placebo to match each of the tablets in the third range is presented, in which the drug substance is replaced by an appropriate amount of calcium hydrogen phosphate.

The oral solution contains vandetanib, hydrochloric acid and purified water.

## **10.6 STABILITY AND STORAGE**

ZD6474 tablets must be stored at temperatures of up to 25C, and used before the expiry date stated on the label. Vandetanib tablets are packaged high density polyethylene (HDPE) bottles and oral solution presented in Type 1. Bottles are sealed with ethylene tetrafluoroethylene (ETFE) copolymer coated chlorobutyl stoppers secured with screw on caps. Each bottle is intended for single use only.

## **10.7 DOSAGE AND ADMINISTRATION**

300mg/day administered orally. The drug should be taken with food and water to minimize GI effects. The tablets should not be taken with grapefruit juice. Tablets should not be crushed, chewed or otherwise divided and must be swallowed whole. Dose modifications will follow the scheme outlined in section 3.3.

## **10.8 REPORTED ADVERSE EVENTS AND POTENTIAL RISKS**

The following adverse events have been reported in patients treated with ZD6474 in phase I and II trials: Rash (including serious complications of progression to desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, and erythema multiforme), pruritis, diarrhea, constipation, nausea and vomiting, dyspepsia, anorexia, dehydration, weight loss, colitis, intestinal ischemia, intestinal perforation, small bowel obstruction, stomatitis, ECG abnormalities (ST and T wave changes, QTc prolongation), hypertension, congestive heart failure, increased serum LDH, hypoalbuminemia, elevation of AST/ALT/GGT/alkaline phosphatase, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypophosphatemia), elevation of serum creatinine hypertriglyceridemia,, headache, dizziness, anxiety, depression, insomnia, confusion, tinnitus, hypoacusis, rhinitis, nasopharyngitis, infections, leukopenia, anemia, thrombocytopenia, bleeding (gingival bleeding, hemoptysis and intracranial hemorrhage), deep venous thromboses and pulmonary embolism, arterial ischemic events (myocardial infection, stroke, peripheral arterial ischemia) fatigue, asthenia, arthralgia, abdominal pain, back pain, fever , cough, dyspnea, interstitial lung disease, peripheral edema, hematuria, proteinuria, dysuria

## **10.9 POTENTIAL DRUG INTERACTIONS**

ZD6474 should not be administered in patients receiving drugs with known significant CYP3A4 inducer effects or with drugs known to prolong QT interval or torsades de point

## **10.10 AVAILABILITY**

ZD6474 is an investigational agent supplied to investigators by Astra-Zeneca, Inc under a CRADA.

## **10.11 AGENT ORDERING**

ZD6474 may be requested from Astra-Zeneca, Inc. by the Principal Investigator (or their authorized designees).

#### **10.12 AGENT ACCOUNTABILITY**

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of drug received from Astra-Zeneca, Inc. using the NCI Drug Accountability Record Form.

## 11 REFERENCES

- 1 Linehan WM, Zbar B, Klausner R. Renal carcinoma. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease. 8th edn. New York: McGraw-Hill, 2001:907–29.
- 2 Linehan WM, Zbar B, Klausner R. Renal Carcinoma. In: Vogelstein B, Kinzler K, eds. The genetic basis of human cancer. 2 edn. New York: McGraw-Hill, 2002.
- 3 Linehan WM, Lerman MI, Zbar B. Identification of the von Hippel-Lindau (VHL) gene. Its role in renal cancer. *JAMA* 1995; 273: 564–70.
- 4 Clifford SC, Maher ER. Von Hippel-Lindau disease: clinical and molecular perspectives. *Adv Cancer Res* 2001; 82: 85–105.
- 5 Maher ER, Kaelin WG Jr. von Hippel-Lindau disease. *Medicine (Baltimore)* 1997; 76: 381–91.
- 6 Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer* 2002; 2: 673–82.
- 7 Maddock IR, Moran A, Maher ER, et al. A genetic register for von Hippel-Lindau disease. *J Med Genet* 1996; 33: 120–27.
- 8 Richard S, Campello C, Taillandier L, Parker F, Resche F. Haemangioblastoma of the central nervous system in von Hippel-Lindau disease. French VHL Study Group. *J Intern Med* 1998; 243:547–53.
- 9 Lonser RR, Weil RJ, Wanebo JE, DeVroom HL, Oldfield EH. Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. *J Neurosurg* 2003; 98: 106–116.
- 10 Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of central nervous system hemangioblastomas in patients with von Hippel-Lindau disease. *J Neurosurg* 2003; 98: 82–94.
- 11 Dollfus H, Massin P, Taupin P, et al. Retinal hemangioblastoma in von Hippel-Lindau disease: a clinical and molecular study. *Invest Ophthalmol Vis Sci* 2002; 43: 3067–74.
- 12 Webster AR, Maher ER, Moore AT. Clinical characteristics of ocular angiomas in von Hippel-Lindau disease and correlation with germline mutation. *Arch Ophthalmol* 1999; 117: 371–78.
- 13 Hammel PR, Vilgrain V, Terris B, et al. Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d’Etude de la Maladie de von Hippel-Lindau. *Gastroenterology* 2000; 119: 1087–95. hemangioblastoma: case report. *Neurosurgery* 1994; 34: 353–55.
- 14 Lubensky IA, Pack S, Ault D, et al. Multiple neuroendocrine tumours of the pancreas in von Hippel-Lindau disease patients: histopathological and molecular genetic analysis. *Am J Pathol* 1998; 153: 223–31.
- 15 Neumann HP, Dinkel E, Brambs H, et al. Pancreatic lesions in the von Hippel-Lindau syndrome. *Gastroenterology* 1991; 101:465–71.
- 16 Hough DM, Stephens DH, Johnson CD, Binkovitz LA. Pancreatic lesions in von Hippel-Lindau disease: prevalence, clinical significance, and CT findings. *AJR Am J Roentgenol* 1994; 162:1091–94.
- 17 Libutti SK, Choyke PL, Alexander HR, et al. Clinical and genetic analysis of patients with pancreatic neuroendocrine tumours associated with von Hippel-Lindau disease. *Surgery* 2000; 128:1022–27.

- 18 Walther MM, Reiter R, Keiser HR, et al. Clinical and genetic characterization of pheochromocytoma in von Hippel-Lindau families: comparison with sporadic pheochromocytoma gives insight into natural history of pheochromocytoma. *J Urol* 1999; 162: 659–64.
- 19 Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumour suppressor gene. *Science* 1993; 260: 1317–1320.
- 20 Knudson AGJ. Genetics of human cancer. *Ann Rev Genet* 1986; 20:231–51.
- 21 Lee S, Chen DY, Humphrey JS, Gnarra JR, Linehan WM, Klausner RD. Nuclear/cytoplasmic localization of the von Hippel-Lindau tumour suppressor gene product is determined by cell density. *Proc Natl Acad Sci USA* 1996; 93: 1770–75.
- 22 Ohh M, Kaelin WG Jr. The von Hippel-Lindau tumour suppressor protein: new perspectives. *Mol Med Today* 1999; 5: 257–63.
- 23 Pause A, Lee S, Worrell RA, et al. The von Hippel-Lindau tumoursuppressor gene product forms a stable complex with human CUL-2, a member of the Cdc53 family of proteins. *Proc Natl Acad Sci USA* 1997;94: 2156–61.
- 24 Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 1999; 399: 271–75.
- 25 Ferrara N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. *Am J Physiol Cell Physiol*. 280(6):C1358-66 (2001).
- 26 Walther MM, Lubensky IA, Venzon D, Zbar B, Linehan WM. Prevalence of microscopic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma and no renal disease: clinical implications. *J Urol* 1995; 154: 2010–14.
- 27 Walther MM, Choyke PL, Glenn G, et al. Renal cancer in families with hereditary renal cancer: prospective analysis of a tumour size threshold for renal parenchymal sparing surgery. *J Urol* 1999; 161: 1475–79.
- 28 Pavlovich CP, Walther MM, Choyke PL, et al. Percutaneous radio frequency ablation of small renal tumours: initial results. *J Urol* 2002; 167: 10–15.
- 29 Pavlovich CP, Linehan WM, Walther MM. Partial adrenalectomy in patients with multiple adrenal tumours. *Curr Urol Rep* 2001; 2:19–23.
- 30 Baghai M, Thompson GB, Young WF Jr, Grant CS, Michels VV, van Heerden JA. Pheochromocytomas and paragangliomas in von Hippel-Lindau disease: a role for laparoscopic and cortical-sparing surgery. *Arch Surg* 2002; 137: 682–88.
- 31 Libutti SK, Choyke PL, Bartlett DL, et al. Pancreatic neuroendocrine tumours associated with von Hippel-Lindau disease: diagnostic and management recommendations. *Surgery* 1998; 124: 1153–59.
- 32 Wedge SR, Ogilvie DJ, Dukes M et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res*. 62:4645-55 (2002).
- 33 Ciardiello F, Caputo R, Damiano V et al. Antitumor effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against epidermal growth factor receptor tyrosine kinase. *Clin Cancer Res*. 9:1546-56 (2003).
- 34 ZD6474 Investigator’s brochure. US Drug Development, Astra-Zeneca Pharmaceuticals. Wilmington, DE.
- 35 Esser N, Marmé D, Drevs J, Konerding MA, Wolloscheck T, Wedge SR, et al. The VEGF receptor tyrosine kinase inhibitor, vandetanib, inhibits angiogenesis and affects

microvascular architecture within an orthotopically implanted renal cell carcinoma. *Clin Cancer Res* 2003;9(Pt 2):6150s

36 Minami H, Ebi H, Tahara M, et al. A phase I study of oral VEGF receptor tyrosine kinase inhibitor ZD6474, in Japanese patients with solid tumors. Proceedings of the American Society of Clinical Oncology, Abstract #778 (2003).

37 R. B. Natale, D. Bodkin, R. Govindan, B. Sleckman, N. Rizvi, A. Capo, P. Germonpré, P. Stockman, S. Kennedy, M. Ranson. *JCO*; 24, 18S (June 20 Supplement) Abstract 7000, (2006)

38 J. V. Heymach, B. E. Johnson, D. Prager, E. Csada, J. Roubec, M. Pešek, I. Špásová, J. Hou, S. Kennedy, R. S. Herbst. *JCO*; 24, 18S (June 20 Supplement), Abstract 7016 (2006)

39 K. Nakagawa, K. Kiura, T. Shinkai, K. Eguchi, Y. Ohe, N. Yamamoto, M. Tsuboi, S. Yokota, M. Fukuoka, H. Jiang. *JCO*; 24, 18S (June 20 Supplement), Abstract 7067 (2006)  
S. Wells, Y. N. You, V. Lakhani, J. Hou, P. Langmuir, D. Headley, M. Skinner, M. Morse, W. Burch, M. Schlumberger. *JCO*; 24, 18S (June 20 Supplement), Abstract 5533 (2006)41

Bertolini, F, Shaked, Y, Mancuso, P, and Kerbel, R.S. The multifaceted circulating endothelial cell in cancer: towards marker and target identification. *Nat. Rev. Cancer*. 6:835-845, 2006.

42 Chung, E. J., Lee, S., Sausville, E. A., Ryan, Q., Karp, J. E., Gojo, I., Telford, W. G. Lee, M.-J., Kong, H. S. and Trepel, J.B. Histone deacetylase inhibitor pharmacodynamic analysis by multiparameter flow cytometry. *Ann. Clin. Lab. Sci.* 35:397-406, 2005.

43 Chung, E. J., Lee, M.-J., Lee, S., Trepel, J. B. Assays for pharmacodynamic analysis of histone deacetylase inhibitors. *Expert Opin. Drug Metab. Toxicol.* 2:213-230, 2006.

44 Posadas, E. M., Gulley, J., Arlen, P. M., Trout, A., Parnes, H. L., Wright, J., Lee, M. J., Chung, E. J., Trepel, J. B., Sparreboom, A., Chen, C., Jones, E., Steinberg, S. M., Daniels, A., Figg, W. D., and Dahut, W. L. A phase II study of perifosine in androgen independent prostate cancer. *Cancer Biol. Ther.* 4:1133-1137, 2005.

45 Gojo, I, Jiemjit, A., Trepel, J. B., Sparreboom, A., Figg, W. D., Rollins, S., Tidwell, M. L., Greer, J., Chung, E. J., Lee, M.-J., Gore, S. D., Sausville, E. A., Zwiebel, J., and Karp, J. E. Phase I and pharmacological study of MS-275, a histone deacetylase inhibitor, in adults with refractory and relapsed acute leukemias. *Blood* 109:2781-2790, 2007.

46 Chung, E. J. and Trepel, J.B. Pharmacodynamic assays using flow cytometry. E-094-2004. Patent in National Phase of Foreign Filing in US, EU, Canada and Australia: Approved for National Phase filing, 7.21.06.

47 Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, Zeiher AM, Dimmeler S: Number and migratory activity of circulating endothelial progenitors cells inversely correlate with risk factors for coronary heart disease. *Circ Res* 89:e1-e7, 2001.

48 Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 2003;348: 593-600.



## **12 APPENDICES**

### **12.1 APPENDIX A: ECOG PERFORMANCE STATUS**

<b>Grade</b>	<b>Scale</b>
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

## 12.2 APPENDIX B: NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

<b>Class</b>	<b>Symptoms</b>
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

### 12.3 APPENDIX C: MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES (TdP) (UPDATED 19 AUGUST 2011)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1. Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

- Concomitant use of these drugs is not allowed during the study or within 2 weeks of study entry (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment:

Table 1 Group 1 Drugs		
Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Amiodarone	Anti-arrhythmic (heart rhythm)	F>M, TdP Cases in Literature
Arsenic trioxide	Anti-cancer (leukaemia)	TdP Cases in Literature
Astermizole	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepidil	Anti-anginal (heart pain)	F>M
Chlorpromazine	Anti-psychotic/antiemetic (schizophrenia/nausea)	TdP Cases in Literature
Chloroquine	Anti-malaria (malaria infection)	
Cisapride	GI stimulant (stimulates GI motility)	Open Prescription Restricted F>M
Clarithromycin	Antibiotic / bacterial infection	
Disopyramide	Anti-arrhythmic (heart rhythm)	F>M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Domperidone	Anti-nausea (nausea)	
Droperidol	Sedative/hypnotic (anaesthesia adjunct)	TdP Cases in Literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F>M
Halofantrine	Anti-malarial (malaria infection)	F>M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F>M
Levomethadyl	Opiate agonist (narcotic dependence)	
Mesoridazine	Anti-psychotic	

Table 1 Group 1 Drugs		
Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
	(schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F>M
Moxifloxacin	Antibiotic / bacterial infection	
Pentamidine	Anti-infective (pneumocystis pneumonia)	F>M
Pimozide	Anti-psychotic (Tourette's tics)	F>M, TdP Cases in Literature
Probucol	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F>M
Sotalol	Anti-arrhythmic (heart rhythm)	F>M
Sparfloxacin	Antibiotic (bacterial infection)	
Terfenadine	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine <sup>8</sup>	Anti-psychotic (schizophrenia)	

Group 2. Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes

Concomitant use of these drugs is not allowed at study entry or within 2 weeks of study entry. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes

Table 2 Group 2 Drugs		
Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Alfuzocin	Alpha 1-blocker (Benign prostatic hyperplasia)	
Amantadine	Dopaminergic/Anti-viral/Anti- infective (Parkinson's disease)	
Atazanavir	Protease inhibitor / HIV	
Azithromycin	Antibiotic (bacterial infection)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Dolastron	Anti-nausea (nausea and vomiting)	
Dronedarone	Anti-arrhythmic / Atrial Fibrillation	

Table 2 Group 2 Drugs		
Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Escitalopram	Anti-depressant / Major depression/ Anxiety disorders	
Famotidine	H2-receptor antagonist / Peptic ulcer/ GERD	
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	
Lapatinib	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nilotinib	Anti-cancer / Leukemia	
Octreotide	Endocrine (acromegaly/carcinoid diarrhoea)	
Ofloxacin		
Ondansetron	Anti-emetic (nausea and vomiting)	
Oxytocin	Oxytocic / Labor stimulation	
Paliperidone	Antipsychotic, atypical / Schizophrenia	
Perflutren lipid microspheres	Imaging contrast agent / Echocardiography	
Quetiapine	Anti-psychotic (schizophrenia)	
Ranolazine	Anti-anginal / chronic angina	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Sertindole	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sunitinib	Anti-cancer / RCC, GIST	
Tacrolimus	Immune suppressant	TdP Cases in Literature
Tamoxifen	Anti-cancer (breast cancer)	

Table 2 Group 2 Drugs		
Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

## 12.4 APPENDIX D: LIST OF DRUGS INTERACTING WITH CYP3A4

This list is only intended as a guide. The impact on the CYP3A4 system of each individual drug administered to patients on this trial should be independently verified

List of Drugs with known interactions with CYP3A4

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	Trade Name	Generic Name	Trade Name	Generic Name	Trade Name
Acetaminophen	Tylenol	Clotrimazole	Mycelex troches	Dexamethasone	Decadron
Carbamazepine	Tegretol	Ketoconazole	Nizoral	Phenytoin	Dilantin
Quinidine	Cardioquin	Troleandomycin	TAO	Rifampin	Rifadin, Rimactane
Cyclosporin	Neoral, Sandimmune	Cyclosporine	Neoral, Sandimmune	Troleandomycin	TAO
Digitoxin	Lanoxin	Itraconazole	Sporanox	St. John's Wort	
Steroids: e.g. Dexamethasone Hydrocortisone Prednisone	Decadron Solu-Cortef Orasone	Erythromycin	Erythrocin		
Diazepam	Valium	Clarithromycin	Biaxin		
Erythromycin	Erythrocin	Nefazodone	Serzone		
Felodipine	Plendil	Grapefruit juice	> 1 quart/day		
Fluoxetine	Prozac	HIV Protease Inhibitors: e.g. Indinavir Nelfinavir Ritonavir Saquinavir	Crixivan Viracept Norvir Fortovase, Invirase		
Nifedipine	Adalat, Procardia	Grapefruit Juice			
Saquinavir	Fortovase, Invirase				
Fexofenadine	Allegra				
Triazolam	Halcion				
Verapamil	Calan				
Warfarin	Coumadin				

### Expanded list of drugs interacting with CYP3A4

Substrates			
Antipyrine	Digitoxin	Methadone	Salmeterol
Astemizole	Diltiazem	Mibefradil	Saquinavir
Atorvastatin	Disopyramide	Miconazole	Sertindole
Benzphetamine	Docetaxel	Midazolam	Sertraline
Bepridil	Dolasetron	Mifepristone	Sibutramine
Bexarotene	Donepezil	Mirtazapine (N-demethylation)	Sildenafil citrate
Bromazepam	Doxorubicin	Montelukast	Simvastatin
Bromocriptine	Doxycycline	Navelbine	Sirolimus
Budesonide	Dronabinol	Nefazodone	Sufentanil
Bupropion (minor)	Enalapril	Nelfinavir	Tacrolimus
Buspirone	Erythromycin	Nevirapine	Tamoxifen
Busulfan	Estradiol	Nicardipine	Temazepam
Caffeine	Ethinyl estradiol	Nifedipine	Teniposide
Cannabinoids	Ethosuximide	Niludipine	Terfenadine
Carbamazepine	Etoposide	Nimodipine	Testosterone
Cevimeline	Exemestene	Nisoldipine	Tetrahydrocannabinol
Cerivastatin	Dofetilide (minor)	Nitrendipine	Theophylline
Chlorpromazine	Felodipine	Omeprazole (sulfonation)	Tiagabine
Cimetidine	Fentanyl	Ondansetron	Tolterodine
Cisapride	Fexotenadine	Oral contraceptives	Toremifene
Citalopram	Finasteride	Orphenadrine	Trazodone
Clarithromycin	Fluoxetine	Paclitaxel	Tretinoin
Clindamycin	Flutamide	Pantoprazole	Triazolam
Clomipramine	Glyburide	Pimozide	Troglitazone
Clonazepam	Granisetron	Pioglitazone	Troleandomycin
Clozapine	Halofantrine	Pravastatin	Venlafaxine (N-demethylation)
Cocaine	Hydrocortisone	Prednisone	Verapamil
Codeine (demethylation)	Hydroxyarginine	Progesterone	Vinblastine Vincristine
Cortisol	Ifosfamide	Proguanil	Warfarin (R-warfarin)
Cortisone	Imipramine	Propafenone	Yohimbine
Cyclobenzaprine	Indinavir	Quercetin	Zaleplon (minor pathway)
(demethylation)	Isradipine	Quetiapine	Zatoestron
Cyclophosphamide	Itraconazole	Quinidine	Zileuton
Cyclosporine	Ketoconazole	Quinine	Ziprasidone
Dapsone	Lansoprazole (minor)	Repaglinide	Zolpidem
Dehydroepiandrosterone	Letrozole	Retinoic acid	Zonisamide
Delavirdine	Levobupivacaine	Rifampin	
Desmethyldiazepam	Lidocaine	Risperidone	
Dexamethasone	Loratadine	Ritonavir	
Dextromethorphan (minor, N-demethylation)	Losartan		
Diazepam(minor;hydroxylation, N-demethylation)	Lovastatin		



<b>Inhibitors</b>			
Amiodarone	Dirithromycin	Metronidazole	Quinine
Anastrozole	Disulfiram	Mibefradil	Quinupristin and
Azithromycin	Entacapone (high	Miconazole	dalfopristin
Cannabinoids	dose)	(moderate)	Ranitidine
Cimetidine	Erythromycin	Nefazodone	Ritonavir
Clarithromycin	Ethinyl estradiol	Nelfinavir	Saquinavir
Clotrimazole	Fluconazole (weak)	Nevirapine	Sertindole
Cyclosporine	Fluoxetine	Norfloxacin	Sertraline
Danazol	Fluvoxamine	Norfluoxetine	Troglitazone
Delavirdine	Gestodene	Omeprazole (weak)	Troleandomycin
Dexamethasone	Grapefruit juice	Oxiconazole	Valproic acid (weak)
Diethyldithiocarbamate	Indinavir	Paroxetine (weak)	Verapamil
Diltiazam	Isoniazid	Propoxyphene	Zafirlukast
	Itraconazole	Quinidine	Zileuton

<b>Inducers</b>			
Carbamazepine	Nelfinavir	Phenytoin	St John's wort
Dexamethasone	Nevirapine	Primidone	Sulfadimidine
Ethosuximide	Oxcarbazepine	Progesterone	Sulfinpyrazone
Glucocorticoids	Phenobarbitol	Rifabutin	Troglitazone
Griseofulvin	Phenylbutazone	Rifampin	
Nafcillin		Rofecoxib (mild)	

## **12.5 APPENDIX E: DIAGNOSTIC CRITERIA FOR VON HIPPEL-LINDAU**

**A diagnosis of VHL can be made under the Following Circumstances:**

**A) Presence of a VHL germline mutation described in VHL families  
OR**

**B) The following clinical circumstances**

**i) With positive family history**

Presence of one or more diagnostic Lesion(s)

- CNS hemangioblastoma
- Renal Cell Carcinoma, multifocal
- Pheochromocytoma
- Retinal angioma
- Pancreatic cysts
- Epididymal cystadenoma

**ii) Without VHL family history**

Presence of CNS hemangioblastomas  
and/or  
Retinal angiomas

If just one of the above, then one of either:

- Renal Cell carcinoma
- Pheochromocytoma
- Epididymal cystadenoma
- Pancreatic cysts / tumor

From: Gladys Glenn, Peter Choyke, Berton Zbar and Marston Linehan. von Hippel-Lindau Disease: Clinical Review and Molecular Genetics. *Problems in Urology*, 1990, 4 (2):132.