Abbreviated Title: Vandetanib/Metformin in RCC
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Title: Phase I/II Trial of Vandetanib in Combination with Metformin in Subjects with HLRCC or SDH-Associated Kidney Cancer or Sporadic Papillary Renal Cell Carcinoma

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Investigational Agents: None

Commercial Agents:

- Vandetanib will be supplied by the manufacturer, Sanofi Genzyme
- Metformin will be purchased from commercial sources by the NIH CC Pharmacy

PRÉCIS

Background:

- The management of advanced renal cell carcinoma (RCC) continues to remain a challenge, particularly for patients with papillary and non-clear cell variants of RCC, for whom there is no standard therapy of proven benefit.
- Inactivation of the Krebs cycle enzyme Fumarate Hydratase (FH) in tumors associated with hereditary leiomyomatosis and renal cell cancer (HLRCC) results in a metabolic shift characterized by a) reliance on aerobic glycolysis for energy production, b) upregulation of HIF 1-α and its downstream targets that promote glucose delivery and uptake to fuel aerobic glycolysis, and c) downregulation of AMPK, resulting in activation of the mTOR pathway and increased macromolecule synthesis.
- Inactivation of another Krebs cycle enzyme, Succinate Dehydrogenase (SDH), is also associated with a familial form of kidney cancer which shares some of the above metabolic features.
- Vandetanib is a dual VEGFR/EGFR inhibitor that reverses the metabolic phenotype associated with FH (and SDH) inactivation and has potent preclinical activity in FH-/- and SDH -/- tumors. Metformin activates AMPK and has demonstrated potent synergy when combined with vandetanib, in preclinical models of FH -/- tumors.
- In this phase 1/2 trial, we first propose to establish the safety and dosing parameters of combined vandetanib and metformin therapy. We then propose to test the activity of vandetanib in combination with metformin in patients with HLRCC or SDH-associated RCC, as well as those with sporadic forms of papillary RCC.

Objectives:

Phase I Component:

- Establish the safety and maximum tolerated dose of the combination of vandetanib with metformin in patients with advanced RCC.

Phase II Component:

- Determine the overall response rate (RECIST 1.1) following treatment with combined vandetanib/metformin in patients with 1) advanced RCC associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) or succinate dehydrogenase renal cell carcinoma (SDH-RCC), and 2) advanced sporadic papillary renal cell carcinoma.

Eligibility:

Phase I Component:

- Diagnosis of advanced RCC
- Patients with clear cell RCC must have either declined, be unable to receive, progressed on, or be intolerant of high-dose IL-2 or established first and second line VEGF and/or mTOR targeted agents
- No prior therapy is required in patients with non-clear cell RCC, but prior therapy is allowed

Phase II Component:

- Diagnosis of advanced RCC associated with HLRCC or SDH-RCC (cohort 1) or sporadic/non-HLRCC papillary RCC (cohort 2)
- No more than 2 prior regimens with VEGF-pathway antagonists

General requirements for both Phase I and II:

- Age ≥18
- Brain metastases or spinal cord compression that requires treatment, unless the treatment ended at least 4 weeks before starting protocol therapy and the condition has been stable without steroid treatment for at least 10 days
- No major surgery within four weeks or inadequately healed wounds prior to study enrollment
- Adequate organ function

Design:

Phase I Component:

- Combination vandetanib and metformin will be administered at starting doses of 300 mg QD and 250 mg BID, respectively.
- The study design is based on a single arm, fixed order dose-escalation Phase 1 study using a modified Fibonacci schema.
- Up to 6 patients may be enrolled in a specific dose combination cohort. Based on the assumption that 3 dose levels will be evaluated, the total number of evaluable patients will be 18. To allow for a few patients who may be inevaluable, the accrual ceiling for this portion of the study will be set at 21. Based on how dose escalation proceeds and the adverse events seen, the total number of patients to be accrued may be changed via a protocol amendment.

Phase II Component:

- Once the MTD is determined, the appropriate combination dose will be evaluated in the phase 2 component.
- Patients will be accrued into one of two independent, parallel cohorts:
    - Cohort 1 – Patients with advanced HLRCC or SDH associated RCC.
    - Cohort 2 – Patients with advanced sporadic/non-HLRCC papillary kidney cancer.
- Patients will be evaluated for response every 8-12 weeks using RECIST 1.1.
- The study is based on open label two-stage optimal phase II design.
- The accrual ceiling for this portion of the study will be 21 patients for each cohort.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- *Phase 1 Component*: To establish the safety and maximum tolerated dose (MTD) of vandetanib and metformin when used in combination in patients with metastatic RCC.
- *Phase 2 Component*: To determine the overall response rate (RECIST 1.1) following treatment with the combination of vandetanib and metformin in patients with 1) advanced RCC associated with HLRCC or SDH, and 2) advanced sporadic/non-HLRCC papillary RCC.

1.1.2 Secondary Objectives

- *Phase 1 Component*
    - To evaluate the clinical activity of the combination of vandetanib and metformin.
    - To evaluate modulation of the biochemical and metabolic phenotype following therapy using paired pre- and on-treatment tumor biopsies (when available).
    - To identify drug interaction between metformin and vandetanib at clinically-relevant doses.
- *Phase 2 Component*
    - To assess duration of response, progression-free survival and overall survival with this combination.
    - To investigate the effect of vandetanib/metformin on potential biomarkers of angiogenesis in plasma such as VEGF and soluble VEGFR2.
    - To evaluate modulation of the biochemical and metabolic phenotype following therapy using paired pre- and on-treatment tumor biopsies (when available).
    - To evaluate the prevalence of somatic fumarate hydratase (FH) and succinate dehydrogenase (SDH) mutations/inactivation as well as activation of/mutations in the NRF2/KEAP1/CUL3 pathway in patients with sporadic papillary RCC and to determine if there is a correlation between the presence of a mutation and response.

1.2 BACKGROUND AND RATIONALE

In 2013, kidney cancer was ranked the sixth and eight most common malignancy among American men and women, respectively, with an estimated 65,150 new cases and 13,680 deaths (1). While surgical treatment for localized disease can be curative, the outlook for patients with metastatic disease remains poor. With increased understanding of the molecular pathways involved in the pathogenesis of RCC, several new systemic agents are available for use in metastatic disease, largely for patients with clear cell RCC. Unfortunately, with the exception of high dose interleukin-2, these therapies are not curative and seldom lead to long-term durable responses.

Several subtypes of RCC have been defined according to their histologic appearance, including clear-cell (the most common histologic subtype), papillary, chromophobe, and other less frequently encountered subtypes. Individual subtypes of RCC are characterized by distinct genetic alterations and metabolic properties, which can potentially predict targets for therapeutic

intervention. Recent work has shown that alterations in the critical metabolic pathways of a cell, including those involved in oxygen, nutrient, and energy sensing/utilization are a common theme in most subtypes of RCC.

Glycolysis is a multistep process whereby glucose is converted to pyruvate, a key substrate for the mitochondrial Krebs cycle. Through a multi-enzymatic process, the Krebs cycle produces ATP and NADPH. When oxygen availability is limited, ATP is produced (albeit less efficiently) by the conversion of pyruvate into lactate. In the early 20th century, Dr. Otto Warburg noted that in comparison to normal cells, cancer cells consumed large amounts of glucose and produced lactate even in the presence of oxygen. This phenomenon is referred to as the "Warburg effect" and is thought to result from dysfunctional mitochondria and impaired oxidative phosphorylation, leaving affected cells dependent on ATP generated during the conversion of pyruvate to lactate. The term "aerobic glycolysis" was coined because this process occurred in an oxygen-rich environment. The role of aerobic glycolysis as the exclusive source of ATP in cancer remains a source of debate. Most cancers appear to have a functioning oxidative phosphorylation pathway, while also utilizing aerobic glycolysis to some extent. Our group and others have characterized RCC variants with defects in the Krebs cycle that render these cells reliant on glycolysis for their energy requirements (2).

1.2.1 HLRCC and Papillary RCC

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is a familial syndrome in which affected individuals are at increased risk for the development of papillary renal cell cancer, as well as cutaneous and uterine leiomyomas. Linkage analysis studies have led to the identification of germline mutations in the Krebs' cycle enzyme *fumarate hydratase (FH)* as the genetic event underlying this inherited syndrome (3, 4).

Although kidney cancer occurs less frequently than leiomyomas (approximately one third of patients with HLRCC seen at the National Cancer Institute had kidney cancer), it is usually associated with an aggressive clinical course and poor outcome. Unlike other well described hereditary renal cancer syndromes where multiple bilateral renal tumors are the norm (i.e. von Hippel Lindau disease), most HLRCC patients tend to have solitary renal lesions; however, bilateral, multifocal lesions have been described in some patients.

Renal cell cancer associated with HLRCC is characterized by distinct histopathologic features and clinical course. The tumors tend to metastasize early with a predilection for regional and distant lymph nodes, liver, and bone. There are currently no standard treatment options available for patients with advanced or unresectable disease, with the majority of these patients dying due to metastatic disease. In the past, HLRCC-associated renal tumors have been histologically described as resembling papillary type II or collecting duct tumors. In a recent report, Merino *et al.* have described the distinctive histopathologic features of HLRCC-associated renal tumors based on a review of forty tumors (5). These tumors have characteristic large orangiophilic nuclei and a clear perinuclear halo, with a variety of architectural patterns such as papillary, tubulo-papillary, tubular, solid or mixed.

There is currently no well described sporadic counterpart to HLRCC-associated kidney cancer and no conclusive evidence that somatic FH mutations play a significant role in sporadic kidney cancer tumorigenesis. However, we (investigators in the UOB/NCI) have evaluated several patients with papillary histology whose tumors histologically resemble that of HLRCC-associated renal cancer,

with no accompanying family history, germline FH mutation, or other sequelae of this syndrome. Most pathologists currently offer vague descriptions of these tumors, often characterizing them as papillary type 2 RCC or collecting duct tumors. Evaluation of these non-familial cases of papillary RCC variants for evidence of somatic inactivation of FH is ongoing.

1.2.2 Genetic and Biochemical Basis of Renal Oncogenesis in HLRCC

Patients with HLRCC have a germline mutation in *FH*, localized to the long arm of chromosome 1 (1q42.3-q43). The gene responsible for HLRCC was identified through linkage analysis, and encodes *FH*, a Krebs cycle enzyme. In addition to the germline loss/mutation of one *FH* allele, functional inactivation of the remaining copy of *FH* has also been found in most HLRCC associated renal tumors, cutaneous leiomyomas, and uterine leiomyomas. Correspondingly, tumors in HLRCC patients have been found to have extremely low or absent FH enzymatic activity. Thus, the *FH* gene appears to act as a tumor suppressor gene, following Knudson's "two hit" model of carcinogenesis. Germline mutations are generally due to missense, frameshift, nonsense, or splice site mutations, and are distributed throughout the gene.

Our group has developed the first cell line from an HLRCC-associated kidney cancer (UOK262) and has demonstrated that there is a three-step process involved in renal oncogenesis in FH -/- kidney cancer.

Step 1: Metabolic Shift to Aerobic Glycolysis

When FH is inactivated, the respiratory capacity of the Krebs cycle/electron transport chain is severely compromised. The cell is unable to generate ATP by oxidative phosphorylation, resulting in a dramatic increase in glucose transport and glycolysis to sustain ATP production. The main source of ATP for the FH -/- deficient kidney cancer cell is glycolysis (**Figure 1**); almost all of the glucose that enters the cell is used to generate ATP via glycolysis and very little goes to the Krebs cycle (6).

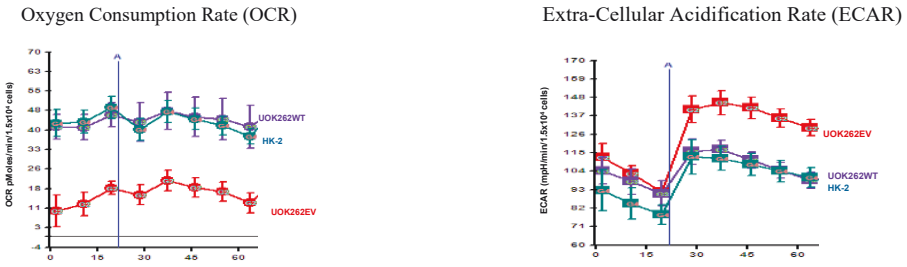


Figure 1: Oxygen consumption is very low in UOK262 versus UOK262WT or control cells (left panel). Extra-cellular acidification (a surrogate for lactate production, i.e., glycolosis) is significantly increased in the HLRCC FH-deficient UOK262 kidney cancer cell line (right panel).

HLRCC-associated fumarate hydratase deficient kidney cancer is the prototypic example of the Warburg effect in cancer; i.e., a cancer that has undergone a metabolic shift to aerobic glycolysis.

Step 2: Inhibition of prolyl hydroxylase leads to an increase in hypoxia inducible factor 1α (HIF1α)

One consequence of FH inactivation is an increase in cellular levels of its substrate, fumarate (7). Increased fumarate inhibits prolyl hydroxylase, which leads to an increase in HIF1α (

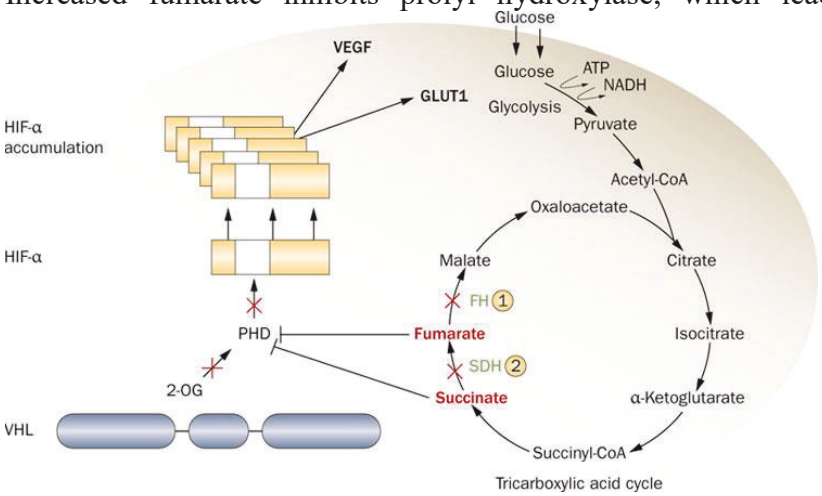


Figure 2). Increased intracellular levels of HIF1α result in transcriptional upregulation of VEGF levels (promoting tumor vasculature/neoangiogenesis) and GLUT1 and GLUT4, which increase glucose uptake for this glucose-dependent tumor. This fact is supported by the demonstration by Pollard *et al*. (by immunochemistry and immunoblotting) that there was strong hypoxia inducible factor-1 (HIF-1) expression in kidney tumors from HLRCC patients (8). Similarly, Isaacs *et al*. demonstrated increased expression of both HIF-1α and HIF-2α in renal tumors from patients with HLRCC compared to normal, matched renal tissue from the same patient (9). In addition, there is also evidence of increased expression of downstream tumorigenic and pro-angiogenic transcriptional targets of HIF. For instance, the observed increase in microvessel density correlated with an increase in expression of *VEGF* mRNA. Furthermore, increased microvessel density is seen in leiomyomas from HLRCC patients, when compared to matched normal myometrium (8).

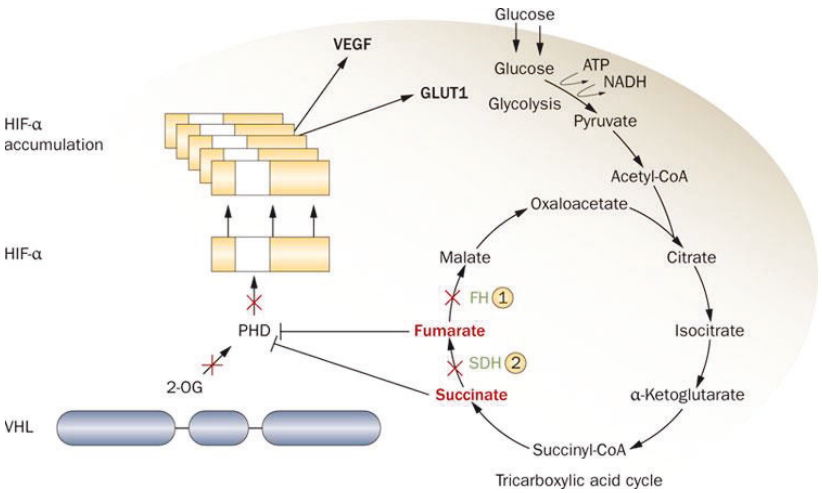


Figure 2. In HLRCC FH-deficient kidney cancer, fumarate is increased and the increased fumarate inhibits prolyl

hydroxylase, which results in HIF accumulation and increased VEGF and GLUT1 and GLUT4 in the tumor. (2010 Nature Rev Urol)

Step 3: Increased ATP production by glycolysis decreases AMPK, which, in turn, increases fatty acid synthesis and stimulates mTOR.

We have recently shown that the increased ATP production by glycolysis in fumarate hydratase-deficient kidney cancer causes a decrease in the both the levels of and phosphorylation of the primary energy sensing complex in the cell, AMPK. Decreased AMPK, in turn, activates the mTOR pathway and fatty acid synthesis (**Figure 3**) (10). This metabolic shift in FH -/- kidney cancer results in an extremely aggressive kidney cancer phenotype.

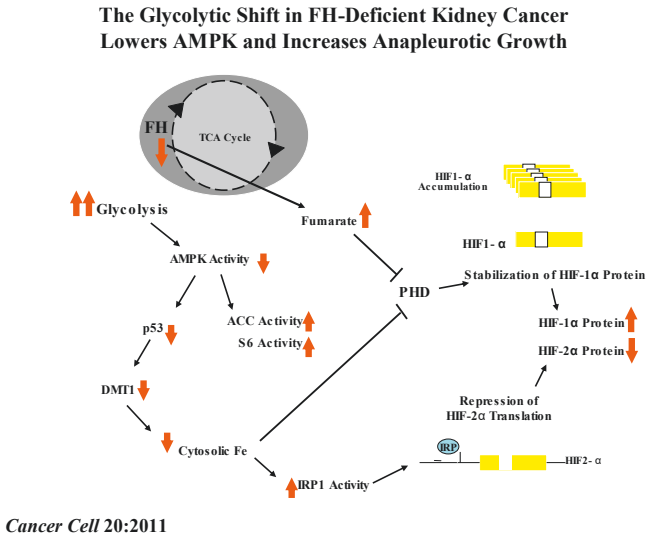


Figure 3.The increased ATP production by increase glycolysis in the glucose-dependent HLRCC FH-/- kidney cancer cells decreases AMPK, activates mTOR, increases fatty acid production and further stabilizes increased levels of HIF1α.

Succinate Dehydrogenase Renal Carcinoma (SDH-RCC)

Succinate Dehydrogenase Renal Carcinoma (SDH-RCC) is a syndrome related to hereditary paraganglioma (PGL) in which patients are at risk for the development of pheochromocytoma, paraganglioma, and kidney cancer. SHD-RCC is characterized by germline mutation of the Krebs cycle enzyme *succinate dehydrogenase*. The SDH enzyme is an inner mitochondrial membrane enzyme critical to the Krebs cycle and the electron transport chain. This enzyme is made up of four subunits (SDHA, SDHB, SDHC, and SDHD) and catalyzes the oxidation of succinate to fumarate. Germline mutations of SHDB, SDHC and SDHD have been found in SDH-RCC families (11, 12). The SDH complex catalyzes the oxidation of succinate to fumarate in the Krebs cycle and serves as complex II in the electron transport chain. We have found that renal tumors associated with this syndrome demonstrate impaired oxidative phosphorylation with reliance on aerobic glycolysis, and are clinically aggressive, as is the case with HLRCC-associated tumors. Tumors associated with SDHB have a distinct morphology with cuboidal cells having “bubbly, eosinophilic cytoplasm” with indistinct cell borders. Our experience is that the biologic basis for

genesis of RCC in these patients is similar to that seen with HLRCC. We have shown that SDH-deficient kidney cancer is characterized by aerobic glycolysis; i.e., the UOK269 SDH-deficient kidney cancer cell line is characterized by very low respiration and significantly increased glycolysis (Rouault et al., personal communication, manuscript in preparation). We hypothesize that both types of kidney cancer might be susceptible to similar therapeutic interventions.

1.2.3 Vandetanib

Vandetanib (ZD6474) is an orally administered receptor tyrosine kinase inhibitor with potent activity against VEGFR2 as well as activity against EGFR (13, 14). This agent is an FDA-approved (2011) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Murine preclinical human xenograft models have demonstrated activity of vandetanib against a variety of tumors including those arising in the lung, prostate, ovary, breast and colon. Reductions 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 (15). The following is a summary of pre-clinical and clinical studies with vandetanib:

In vitro studies

In isolated enzyme assays, vandetanib was found to be a potent inhibitor of KDR tyrosine kinase activity (IC50=40nM), with additional activity against Flt-4 (IC50=110nM) and EGFR (IC50= 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 IC50 ranging from 1μM to >200μM (14).

Vandetanib inhibited the proliferation of both VEGF-stimulated and EGF-stimulated human endothelial cell lines (HUVEC), while basal HUVEC proliferation was not significantly affected (16). When co-cultured with human fibroblasts, endothelial tube formation by HUVEC cells was inhibited at similar concentrations of vandetanib. Direct inhibition of tumor growth was demonstrated against established lung, colon, ovarian, breast, and prostate cancer cell lines, but only at higher concentrations, with IC50s in the 0.6 to 13.5 μM range.

The effect of vandetanib 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 fibers. 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 [(15)]

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 16 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 vandetanib and the N-desmethyl of vandetanib. The drug 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. Vandetanib 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.
- 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, embryo/fetal loss, delayed fetal development, heart vessel abnormalities, and precocious ossification of skull bones reflect the range of reproductive and embryo/fetal 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, vandetanib 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.
- Vandetanib inhibited tumor-associated angiogenesis in athymic mice intradermally implanted with A549 lung cancer cells.
- Vandetanib inhibited tumor vascular flow, volume and permeability as assessed by K trans measurements in established PC-3 prostate tumor xenografts using dynamic contrast-enhanced MRI
- In human tumor xenograft models (lung, prostate, ovary, breast, vulval, colon), vandetanib inhibited the growth of established subcutaneous tumors in mice.
- Tumor regression by vandetanib 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 RCC), administration of vandetanib reduced both primary tumor growth and the incidence of pulmonary metastases.
- Anti-tumor effects of vandetanib 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.

Human Studies

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 vandetanib at 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 at the 100mg and 300mg dose levels, respectively, who were enrolled to better evaluate the effect of vandetanib on QT interval and ST, T wave changes. This study helped establish 300 mg/day as the MTD (17). A second phase I trial of 18 patients conducted in Japan (TVE-15-11) followed a dose escalation pattern evaluating 100, 200, 300 and 400mg daily oral doses. The data from this study suggested that 400 mg/day dose likely exceeded the MTD (18).

Pharmacokinetics

Pharmacokinetic data obtained from the Western and Japanese studies were comparable. Absorption was highly variable, with individual patients having a Tmax as late as 24 hours post-dose. Following achievement of maximum plasma concentration, Cmax 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 Cmax 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:

- 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.
- 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).
- 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.
- Cardiovascular toxicity
    - In the western trial, 6 patients (8%) had T-wave or ST-segment changes consistent with repolarization abnormalities.
    - 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
    - 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/001, 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), which specifically included thrombocytopenia and diarrhea. Later phases of development used doses less than 500mg because plasma levels observed in subjects in the 500 mg group overlapped considerably with those at 600 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 vandetanib.

Withdrawal from Study

Sixty-seven patients were withdrawn from study in the 6474IL/0001 trial and 56 of these withdrawals were a result of disease progression. Six 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 vandetanib could not be ruled out. One patient was withdrawn from protocol due to abnormal QTc prolongation. Three 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 vandetanib (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 vandetanib; four achieved a partial response at doses ranging from 200-300 mg. This data suggested that vandetanib may have activity as monotherapy in otherwise chemoresistant NSCLC and could be equally as efficacious in other cancers.

The data from the Phase I studies confirm that vandetanib 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 vandetanib achieved at steady state with 300 mg cover the theoretical IC50 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 vandetanib 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 vandetanib and had objective responses as evaluated by radiographic studies.

Phase II study results

Several phase II studies involving vandetanib have been performed. A randomized double-blind phase II trial comparing vandetanib monotherapy with gefitinib monotherapy in 168 patients with advanced NSCLC as second or third line therapy demonstrated that patients receiving vandetanib 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 vandetanib 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 vandetanib arm compared with the gefitinib arm, although it is unclear if this increase can be attributed to vandetanib (19).

Another randomized double blind phase II study evaluated PFS in second-line treatment of 127 patients with advanced NSCLC, and demonstrated that vandetanib 100mg or 300mg plus docetaxel increased PFS to 18.7 weeks and 17 weeks, respectively, compared with 12.0 weeks for doctexael plus placebo. No difference in OS was detected between the two arms. The toxicities were similar to those expected in patients treated with docetaxel and those observed in other vandetanib studies, but the vandetanib arm had a greater frequency of rash and asymptomatic QTc prolongation (20).

In another randomized double-blind phase II dose-finding study, 53 Japanese patients with NSCLC were given vandetanib as monotherapy at escalating doses between 100 and 300 mg/day. Results from this study demonstrated a 17.6%, 5.6%, and 16.7% partial response (PR) rate for the 100, 200, and 300 mg/day dosing, respectively, and a 49% disease control rate (PR + stable disease). The toxicity profile was similar to that seen in other trials with vandetanib, although the investigators reported a death related to interstitial lung disease that was considered to be related to vandetanib (21).

Results from a phase II trial to assess objective tumor response in patients with hereditary metastatic medullary thyroid cancer (MTC) having mutations in the *RET* proto-oncogene receiving vandetanib monotherapy (300mg/day) were recently reported. Six of thirty patients (20%) enrolled had a partial response, while an additional 16 patients (53%) demonstrated stable disease for at least 24 weeks. Greater than 50% reduction in the serum tumor markers calcitonin and CEA was observed in 24 and 16 patients, respectively (22). Another phase II trial to evaluate objective tumor response was performed in 19 patients with metastatic MTC, all receiving vandetanib monotherapy at an initial dose of 100 mg/day and escalation to 300 mg/day in the setting of disease progression. Partial responses and stable disease (lasting at least 24 weeks) were seen in 3 (16%) and 10 (53%) patients, respectively. Reductions in serum tumor markers and rates of adverse events were similar to the previously described study (23).

Two phase II trials have also been performed in patients with metastatic breast cancer who have failed first-line therapy. No objective responses were seen in these studies, suggesting minimal clinical benefit of vandetanib in this patient population (24, 25).

Phase III study results

The promising results of the phase II studies of vandetanib in patients with MTC provided the groundwork for a recently published randomized double-blind phase III trial. Over an 11 month period, 331 patients with advanced MTC were randomly assigned in a 2:1 ratio to receive

vandetanib 300 mg/day or placebo with the primary endpoint being PFS based on RECIST criteria. Vandetanib therapy demonstrated significantly improved PFS compared to placebo with a hazard ratio (HR) of 0.46 ($p < 0.01$), as well as advantages in objective response rate, disease control rate, and biochemical response. Overall survival data could not be analyzed because of data were not mature at the point of trial cutoff (26).

Four randomized double-blind phase III studies involving vandetanib in the NSCLC population have also been reported. The most recent study evaluated vandetanib therapy in patients with advanced NSCLC who failed prior therapy with an EFGR inhibitor and prior chemotherapy. Overall, 924 patients received vandetanib 300 mg/day or placebo in a 2:1 ratio with the primary endpoint being OS. Median overall survival was not significantly different between the two groups (8.5 months versus 7.8 months, HR = 0.95, $p = 0.53$), but there was a statistically significant improvement in PFS and objective response rate in the group receiving vandetanib (27).

Another phase III study compared the efficacy of vandetanib versus erlotinib in improving PFS in patients with NSCLC who had failed prior cytotoxic chemotherapy. A total of 1240 patients were randomly assigned to receive vandetanib 300 mg/day (n = 623) or erlotinib 150 mg/day (n = 617). While vandetanib did demonstrate antitumor activity by objective response criteria, there was no advantage of vandetanib therapy in improving PFS compared to erlotinib. Of note, there was a 10% higher rate of grade 3 or higher AEs in the vandetanib group (28).

Finally, two phase III studies sought to evaluate the role of vandetanib use in combination with another agent as second-line therapy in advanced NSCLC. The first study randomized 1391 patients with stage IIIB-IV NSCLC who had failed first-line chemotherapy to vandetanib (100mg/day) + docetaxel versus placebo + docetaxel. Median PFS was significantly longer in the vandetanib/docetaxel group compared to the placebo/docetaxel group (4.0 vs. 3.2 months, respectively; HR = 0.79, $p < 0.0001$) (29). The second trial compared the efficacy of vandetanib (100mg/day) + pemetrexed to placebo + pemetrexed in a similar patient population. Five hundred thirty four patients were randomly assigned in a 1:1 fashion to the aforementioned treatment groups. In contrast to the previous trial, there was no significant difference in PFS between the treatment arms (HR = 0.86, $p = 0.11$), but there was a statistically significant improvement in objective response rate and time to deterioration of symptoms in the arm receiving vandetanib (30).

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

- General – fatigue, weight loss, fever, pain, and asthenia.
- Cardiovascular – Abnormal ECG (with or without QT prolongation; i.e., either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes, ventricular tachycardia, and hypertension.
- Central Nervous System – Headache or dizziness, and reversible posterior leukoencephalopathy syndrome.

- Gastrointestinal – Constipation, diarrhea, non-specific abdominal pain, nausea, gastroesophageal reflux, stomatitis esophageal candidiasis, vomiting, and biliary or bowel obstruction or perforation. Elevated liver function tests were also demonstrated, generally CTC/CTCAE grade 1-2. Preliminary data suggests these are reversible, in some cases even while continuing therapy.
- Hematologic and lymphatic – Ecchymosis, anemia, neutropenia, thrombocytopenia, and hemorrhage.
- Electrolyte and nutritional abnormalities – Anorexia, weight loss, dehydration, hypokalemia, hypomagnesemia and hypophosphatemia.
- Dermatologic – acneiform rash, pruritus, macular or maculopapular rash (generalized or localized), 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 and hand-foot syndrome have also been reported.
- 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, hematuria and renal failure.
- Vascular – Arterial ischemic events (including myocardial infarction, stroke, peripheral ischemia), intracranial bleeding, and venous thromboembolism (including pulmonary embolism). The latter may have ostensibly been due to the hypercoagulability associated with a concurrent neoplastic process or other systemic illness. However, it is considered possible that vandetanib might increase the risk for developing blood clots.
- 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, anorexia, etc.).
- Ophthalmologic – Corneal changes, including ulceration; detached retina.

In addition, a number of other side effects have been reported in clinical trials using vandetanib alone, in combination with other chemotherapy agents or radiation. It is unclear whether these side effects are related to vandetanib, 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
- Left ventricular dysfunction
- Respiratory insufficiency

- 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. Gingival bleeding as well as one case each of hemoptysis and cerebellar hemorrhage has been described in studies with vandetanib, although it is unclear whether these events are attributable to the agent. A recent randomized, placebo-controlled, phase II study of vandetanib in advanced thyroid cancer was performed; 72 subjects were allocated to the vandetanib arm and one of these individuals died from hemorrhage from skin metastases, which was deemed treatment-related (31). Finally, a recent meta-analysis of four randomized controlled trials of vandetanib in non-small cell lung cancer demonstrated no significant difference in the incidence of hemorrhagic events between the subjects receiving vandetanib compared to those receiving other agents (32). While it appears that the risk of hemorrhage attributable to vandetanib is low based on previous studies, the possibility of life-threatening hemorrhage cannot be excluded in subjects receiving this drug.

1.2.4 Combined Blockade of the VEGF and EGFR pathways in HLRCC

The recognition that HIF upregulation may play an important role in the formation and propagation of renal cancer associated with HLRCC suggests that interventions directed against components of this pathway, such as VEGF and TGF-α/EGFR, may be of benefit in this patient population. Additionally, given the exquisite sensitivity of FH-/- cancer cell lines to glucose withdrawal, we hypothesized that therapeutic strategies aimed at limiting glucose delivery to tumors (for instance, targeting tumor vasculature) might be associated with anti-tumor effects.

Our group has explored targeting HIF and its downstream transcriptional targets as a rational therapeutic strategy in HLRCC. We hypothesized that combined VEGF and EGFR-pathway blockade would constrain glucose delivery to tumors and inhibit critical HIF-driven downstream targets. In addition to inhibiting angiogenesis, agents targeting the VEGF axis might permit us to exploit the dependence of these tumors on glucose by impairing delivery of this critical metabolic substrate. Recent evidence suggests that EGFR, in addition to its role as a growth factor receptor, also serves as a heterodimeric partner for SGLT1, a cell surface glucose transporter. Targeting EGFR might, therefore, limit glucose uptake by tumor cells in addition to blunting an important autocrine growth signal.

1.2.5 Vandetanib in combination with Metformin

To our knowledge, there are no studies evaluating the safety or efficacy of vandetanib in combination with metformin administered in multiple doses.

A phase 1 study to assess the pharmacokinetics of single dose metformin when administered in combination with single-dose vandetanib was conducted by the previous manufacturer Astra-Zeneca (Confidential Information). This was a single-center, open-label, nonrandomized, 2 sequential period study to evaluate the plasma metformin concentration-time profiles and the resulting PK parameters in 14 healthy adult male and female volunteers. 13 volunteers received all planned doses of vandetanib and metformin. The primary objective of this study was to assess metformin maximum concentration (C_{max}) and area under the concentration-time curve

extrapolated to infinity (AUC) in healthy volunteers (wild type for OCT2) for metformin administered alone and in combination with vandetanib 800 mg.

On Day 1 in Period 1 volunteers received a single oral dose of metformin 1000 mg alone followed by an at least 7-day washout period. On Day 1 in Period 2, all volunteers received a single oral dose of vandetanib 800 mg alone. Three hours after the dose of vandetanib, all volunteers received a single oral dose of metformin 1000 mg.

On Day 1 in Period 1, volunteers received a light breakfast 4 hours prior to metformin dose and continued to abstain from food until 4 hours postdose. Water was withheld for 1 hour predose until 2 hours postdose. On Day 1 in Period 2, volunteers received a light breakfast 1 hour prior to vandetanib dose and continued to abstain from food until 4 hours after the metformin dose. Water was withheld for 1 hour prior to the vandetanib dose until 2 hours after the vandetanib dose and 1 hour before the metformin dose.

Serial blood samples for PK analysis of metformin were collected for 96 hours following the metformin dose in Period 1. In Period 2, blood samples for PK analysis of vandetanib and metformin were collected for 72 hours and 96 hours following the vandetanib and metformin dose, respectively. Urine was collected for metformin PK in Periods 1 and 2 on Day 1 (continuing through Day 2) from 0 to 24 and 24 to 48 hours following the metformin dose.

In wild-type OCT2 healthy volunteers, exposure to metformin, as assessed by AUC and Cmax, was increased by 74% and 50%, respectively, when vandetanib was given in combination with metformin, a probe substrate for OCT2. The results indicate that vandetanib influences the PK of metformin. Geometric mean metformin CL/F and V_z/F appeared to be lower (by 42% and 39%, respectively) when a single dose of metformin was given with a single dose of vandetanib compared to metformin given alone. There appeared to be no change in metformin geometric mean $t_{1/2,\lambda z}$ and median t_{max}. Coadministration with vandetanib appeared to cause a 52% decrease in geometric mean metformin CL_R. This decrease was observed in all volunteers individually.

Following dosing, there were 15 AEs in 9 (64.3%) volunteers overall. The numbers of volunteers with AEs was higher during the combination treatment than during the metformin alone treatment. However, no clinically relevant differences between the treatments were noted for any individual preferred term.

1.2.6 Preclinical Studies of Vandetanib in Kidney Cancer

Vandetanib Induces Cell Death in FH-Deficient Kidney Cancer with an IC50 16nM

Vandetanib has a unique ability to inhibit invasion as well as viability of UOK262 FH-deficient type 2 papillary kidney cancer with an IC50 of only 16nM. (**Figure 4** and **Figure 5**).

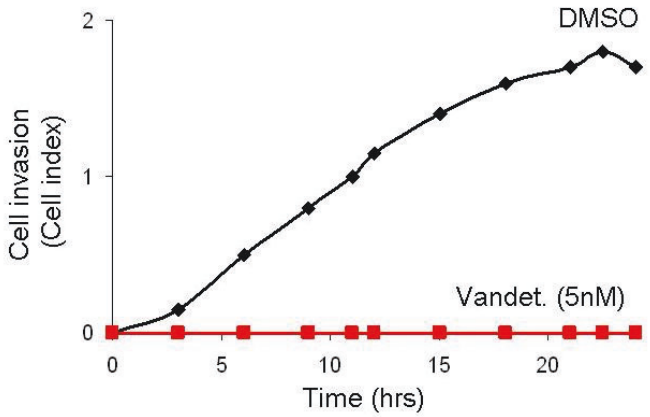


Figure 4: Vandetanib (5nM) significantly inhibits invasion of UOK262 fumarate hydratase deficient type 2 papillary kidney cancer in an *in-vitro* model system.

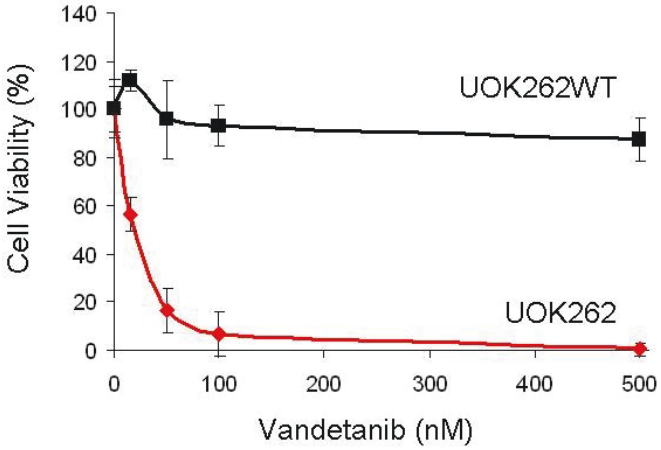


Figure 5. Vandetanib induces death in FH-deficient type 2 papillary kidney cancer, with an IC50 on 16NM. In a synthetic lethal screen, Vandetanib does not affect the viability of UOK262WT, which is the FH-deficient kidney cancer cell line with FH replaced.

Vandetanib Inhibits Glucose Uptake and Reverses the Biochemical Phenotype FH-Deficient Type 2 Papillary Kidney Cancer

Vandetanib reverses the biochemical phenotype in FH-deficient type 2 papillary kidney cancer. Vandetanib decreases glucose uptake, lactate production, ATP production, and increases AMPKα and AMPKβ, which we have shown are essential elements of the metabolic shift in this form of kidney cancer. Vandetanib also decreases the expression of HIF1α and the glucose transporters, GLUT1 and GLUT4 (**Figure 6** and **Figure 7**).

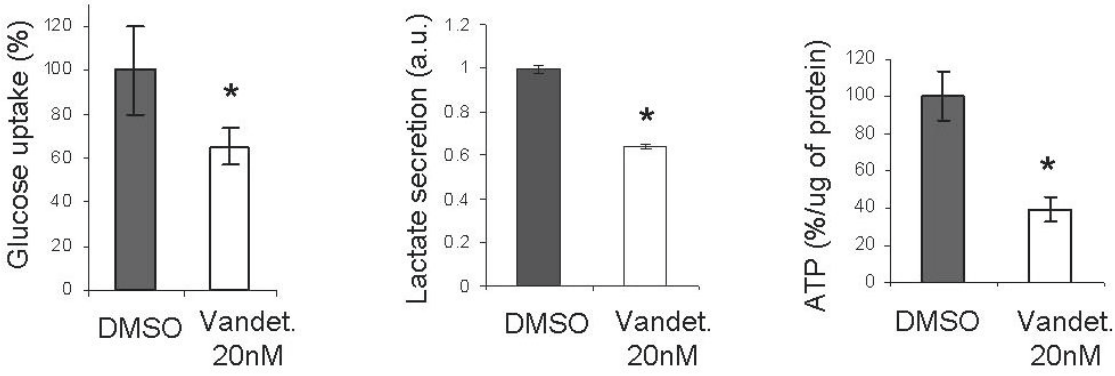


Figure 6. Vandetanib decreases glucose uptake (left panel), decreases lactate secretion (which is a surrogate for glycolysis) (middle panel) and decreases ATP production in UOK262 fumarate hydratase type 2 papillary kidney cancer cell line *in-vitro*.

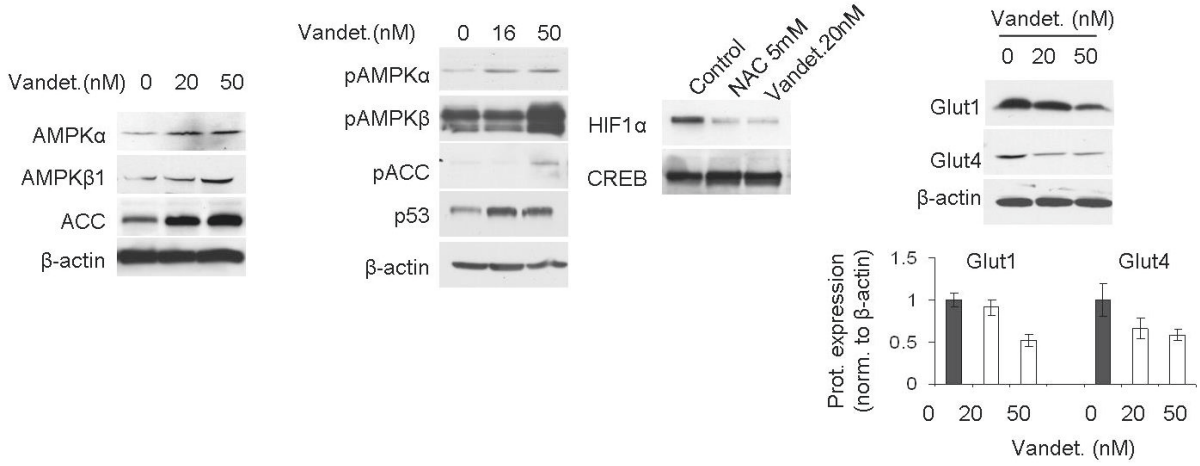


Figure 7. Vandetanib reverses the biochemical metabolic phenotype of UOK 262 fumarate hydratase-deficient type 2 papillary kidney cancer *in-vitro*. With Vandetanib treatment, AMPKα and AMPKβ increase, ACC and PACC increase (indicating a decrease in fatty acid synthesis that is essential for rapid anabolic growth) (upper left and left middle panels). Vandetanib treatment decreases HIF1α (right middle panel) and decreases the expression of the glucose transporters, GLUT 1 and GLUT4 (right upper and lower panels).

Vandetanib Inhibits Cell Viability in SDH-Deficient Kidney Cancer

In order to develop a therapeutic approach to treatment of patients with SDH-deficient kidney cancer, we developed an SDH-deficient kidney cancer cell line model, UOK269, which was derived from a patient with SDHB-deficient kidney cancer. We subsequently developed UOK269WT1 and UOK269WT2, which are cell lines with a "wild type" copy of SDHB replaced. UOK269EV1 and UOK269EV2 are cell lines with "empty vector" to act as a control for UOK269WT1 and UOK269WT2. In synthetic lethal *in-vitro* studies, while vandetanib had little effect on UOK296WT, it significantly inhibited cell viability of UOK269EV (**Figure 8** and **Figure 9**).

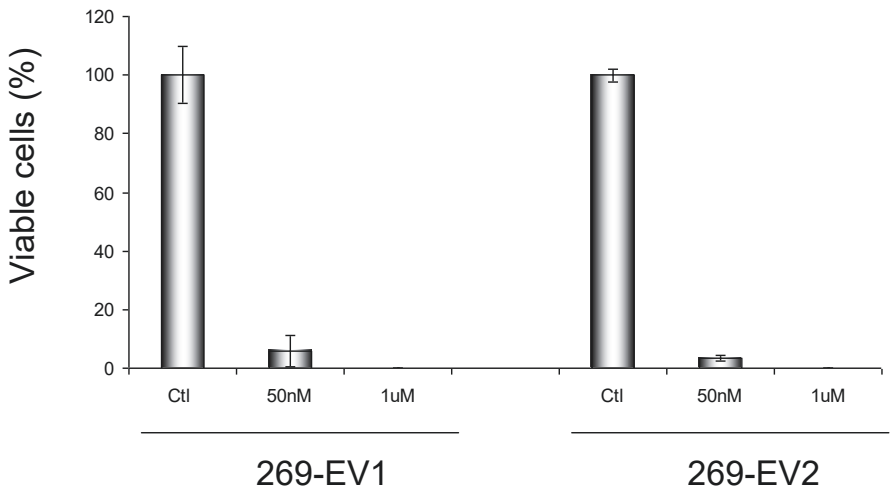


Figure 8. Vandetanib had a significant effect on viability of the succinate dehydrogenase-deficient kidney cancer cell lines, UOK269-EV1 and UOK269-EV2.

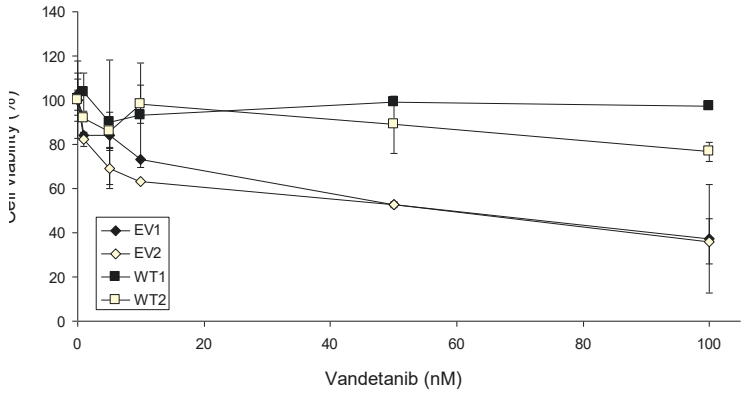


Figure 9. In a synthetic lethal study, while Vandetanib had a significant effect on viability of the succinate dehydrogenase-deficient kidney cancer cell lines, UOK269-EV1 and UOK269-EV2, it had little effect on the UOK269-WT1 and UOK269-WT2 SDHB replaced cell lines.

Vandetanib Induces Complete Regression of Fumarate Hydratase-Deficient Type 2 Papillary Kidney Cancer Xenograft Models

In our *in-vivo,* mouse xenograft models, vandetanib (100mg/kg) induces complete regression of this aggressive form of type 2 papillary kidney cancer (**Figure 10**).

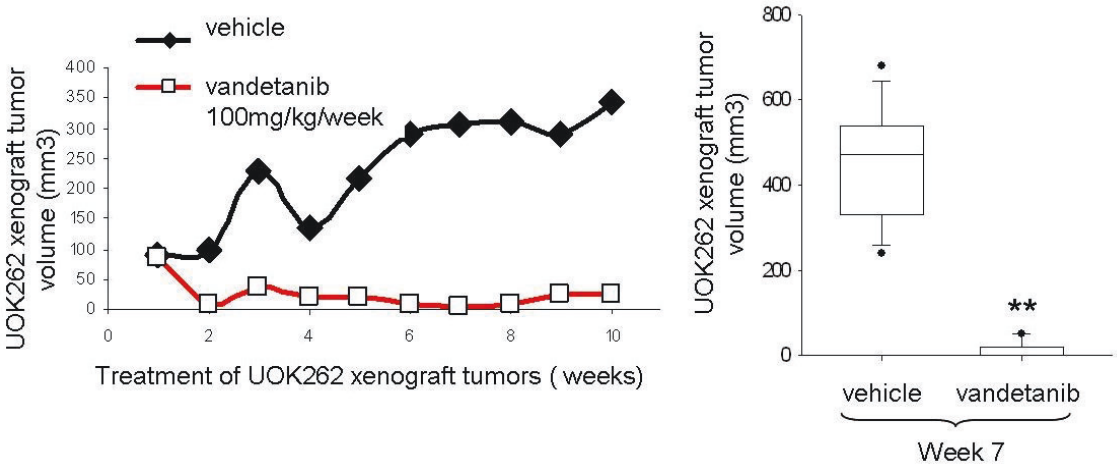


Figure 10. Vandetanib reverses the biochemical metabolic phenotype of UOK 262 fumarate hydratase-deficient type 2 papillary kidney cancer *in-vitro* (left panel). The right panel is the result of two different experiments.

In the xenograft tumors, vandetanib increases AMPKα and AMPKβ, and decreases pS6R (suggesting downregulation or normalization of the mTORC1 pathway). We have shown above that decreased AMPKα and AMPKβ, and increased pS6R are a part of the metabolic shift in FH-deficient type 2 papillary kidney cancer (**Figure 11**). Glut 1 and VEGF-A are also decreased in xenografts from vandetanib-treated mice; secreted VEGF-A is also decreased in serum from xenograft-bearing animals treated with vandetanib (**Figure 12**).

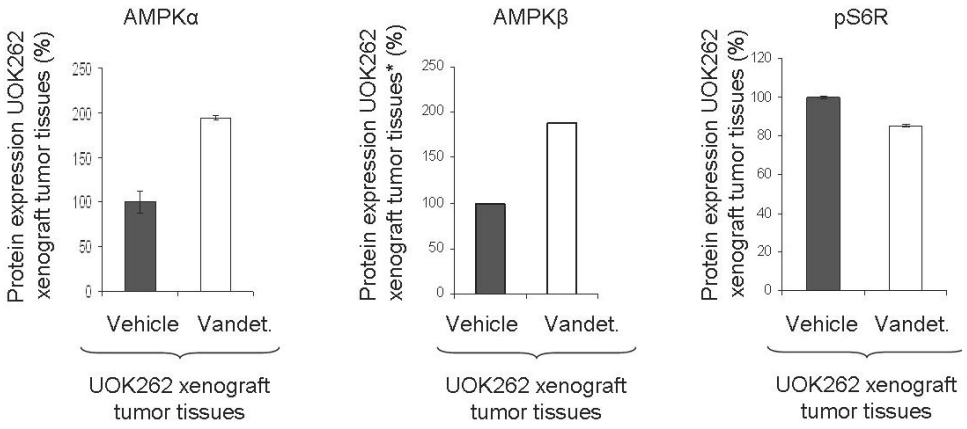


Figure 11. Vandetanib reverses the biochemical metabolic phenotype of UOK 262 fumarate hydratase-deficient type 2 papillary kidney cancer *in-vivo*. With Vandetanib treatment, there is increased AMPKα and AMPKβ and increased pS6R in the xenograft tumors.

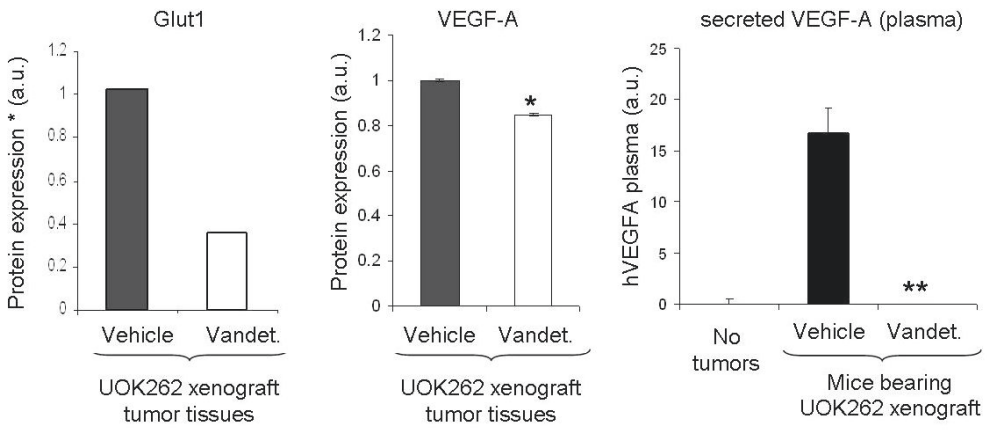


Figure 12. In the Vandetanib-treated mouse bearing the UOk262 fumarate hydratase-defieicnet type 2 papillary kidney cancer there is less GLUT1 and VEFGA expression and there is decreased secreted VEGFA in the serum of the Vandetanib treated xenograft bearing animals.

1.2.7 Role of Metformin in Cancer

Retrospective epidemiologic studies in diabetic patients receiving metformin have shown a reduced lifetime incidence of cancer in this population (33, 34). As a result, metformin and other biguanides are being evaluated as potential anticancer agents. The precise molecular target of metformin is unknown, but it acts to inhibit complex I of the mitochondrial electron transport chain to block oxidative respiration (35). This increases cellular AMP-to-ATP ratios and activates the AMP-activated protein kinase (AMPK) (36). AMPK coordinates the activity of several metabolic and growth pathways that are important in cellular energy balance. For example, AMPK increases GLUT1 expression to promote glucose uptake and phosphorylates phosphofructokinase-2 to promote energy generation through increased glycolysis. Conversely, AMPK phosphorylates proteins such as TSC2 and Raptor (components of the mammalian target of rapamycin [mTOR] cascade) to inhibit protein synthesis and it phosphorylates acetyl-CoA carboxylase to inhibit lipid synthesis, thereby suppressing energy-consuming processes (37, 38).

1.2.8 Synergistic Effects of Metformin and Vandetanib in HLRCC

Preclinical studies with UOK 262 have demonstrated synergistic antitumor activity when vandetanib is combined with metformin (unpublished data). These data provide the basis for evaluating this combination in HLRCC.

Treatment of FH -/- deficient type 2 papillary kidney cancer with metformin reverses the FH -/- biochemical phenotype (i.e., it increases AMPK and inhibits the enzymes that drive fatty acid synthesis) and significantly inhibits HLRCC FH -/- kidney cancer UOK262 cellular invasion (**Figure 13**).

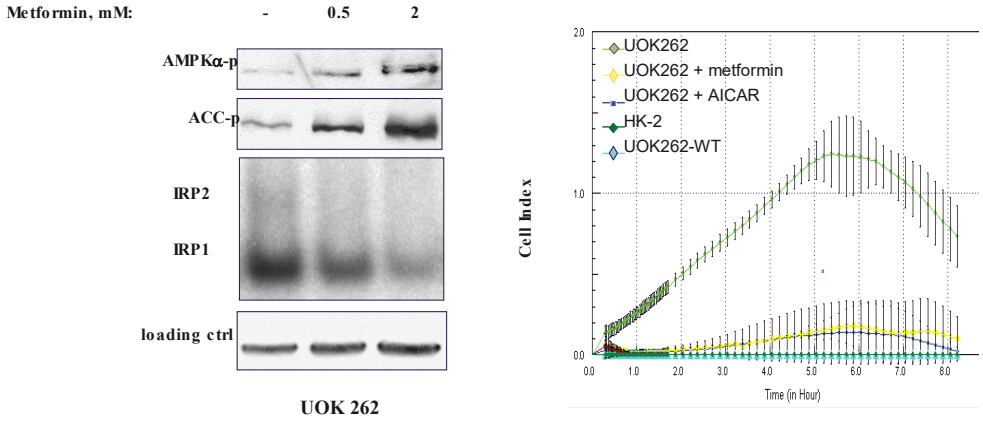


Figure 13. Metformin (and a similar agent which also activates AMPK, AICAR) reverse the biochemical phenotype of FH-deficient kidney cancer; AMPK levels increase and fatty acid synthesis enzymes are decreased (left panel). Metformin and AICAR have a significant effect on in-vitro growth of the fumarate hydratase-deficient kidney cancer cell line, UOK262.

*In vitro***,** we have shown that the combination of metformin and vandetanib has significantly greater effect on cell viability than either agent alone (Figure 14). We have also shown that the combination of metformin plus vandetanib has a greater effect in reversing the biochemical metabolic phenotype of fumarate hydratase-deficient type 2 papillary kidney cancer than either agent alone. The combination has a greater effect in increasing AMPKα, PACC and ACC (which indicate a decrease in fatty acid synthesis) than either agent alone.

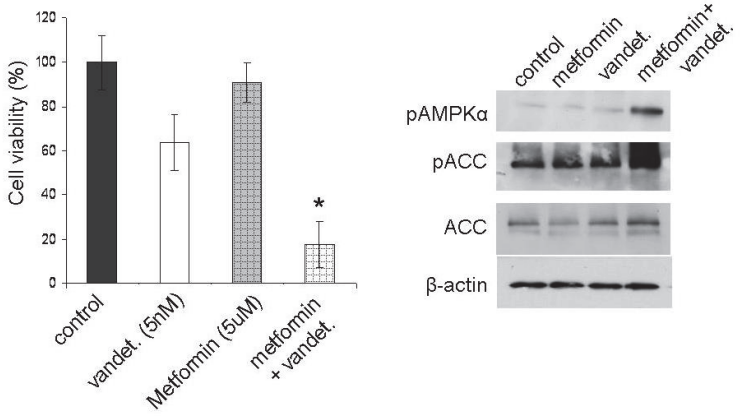


Figure 14. The combination of metformin plus Vandetanib has a greater effect on cell viability (left panel) and on pAMPKα, pACC and ACC (right panel) than either agent alone.

In our *in vivo* models we found significant synergy with metformin plus vandetanib versus vandetanib or metformin alone (**Figure 15** and **Figure 16**). When combined with metformin, vandetanib induces complete tumor regression at doses that are a log lower than those used in single agent vandetanib studies.

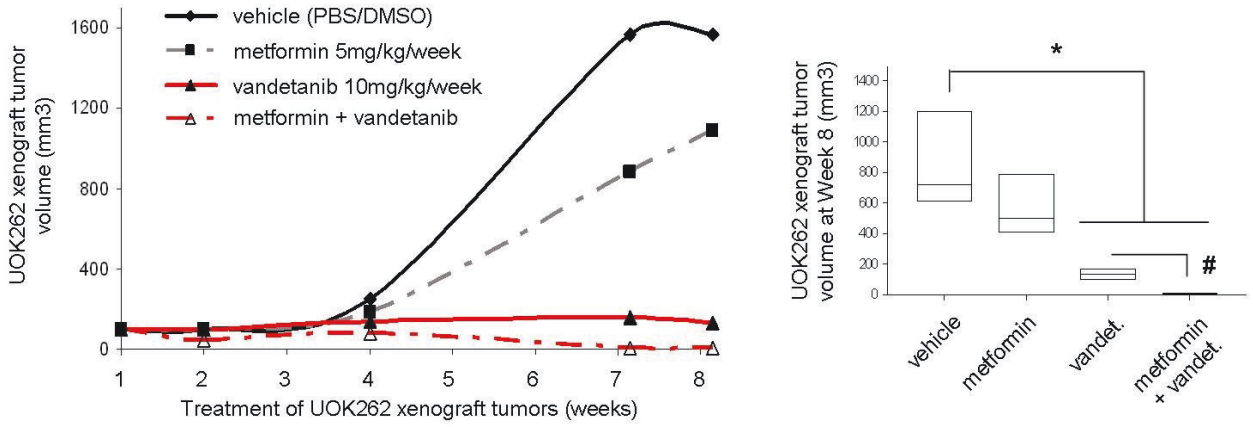


Figure 15. The combination of metformin plus Vandetanib has a greater effect on UOK262 fumarate hydratase-deficient type 2 papillary kidney cancer xenograft tumor growth than either metformin or Vandetanib alone (left panel). The right panel is the sum of two different animal experiments. The dose of Vandetanib in these experiments is 10 mg/kg/week; which is 1/10th the dose used above as a single agent and 1/35th the dose used in published xenograft studies with this agent.

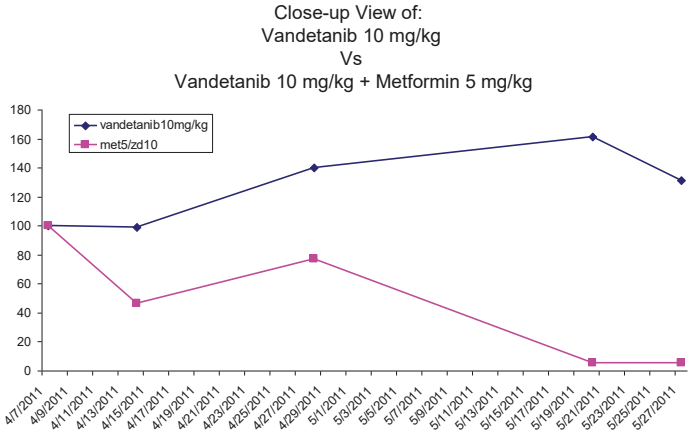


Figure 16. This figure, a close up of from the preceding figure, demonstrates the synergistic effect of the combination of metformin and Vandetanib in the UOK262 fumarate hydratase-deficient type 2 papillary kidney cancer xenograft model. This combination induced complete regression of the tumors.

1.2.9 Rationale and Summary

Despite the availability of several agents with activity in clear cell RCC, there are no standard treatments of proven benefit for patients with advanced papillary RCC. Several agents have been shown to have limited activity in retrospective or small phase II studies involving subjects with advanced papillary RCC. Most recently, the efficacy of foretinib (a dual MET/VEGFR2 inhibitor) in patients with advanced papillary RCC was assessed in a multi-institutional study, which demonstrated a median progression-free survival of 9.3 months (39). Of note, the agent was most effective in those subjects with a germline *MET* mutation, which may limit the applicability of this agent to individuals with this specific mutation. While sunitinib is approved for patients with

advanced kidney cancer, the benefit in patients with non-clear cell histology appears to be limited. Several phase II studies have evaluated the efficacy of sunitinib in patients with papillary RCC, and most demonstrate a median PFS between 1.6 and 6 months, and overall response rates between 0-12%. Temsirolimus also has limited efficacy in advanced papillary RCC, with one study reporting a median PFS of 3.8 months and overall response rate of 5.4%

Patients with HLRCC or SDH associated metastatic RCC as well as most patients with sporadic papillary RCC have particularly aggressive disease that is usually not responsive to currently available targeted agents. Impairment of Krebs cycle function leads to a metabolic switch whereby affected tumor cells are reliant on aerobic glycolysis as the primary source of energy production; since glycolysis is a less efficient means of ATP synthesis than is oxidative phosphorylation, a constant supply of glucose is necessary to fuel the energy needs of the cell. The Krebs cycle substrates of both FH and SDH (fumarate and succinate) inhibit hydroxylation of HIF, leading to an increase in intracellular HIF1α, which augments the angiogenesis pathway via upregulation of VEGF, and glucose uptake via overexpression of GLUT1 and GLUT4. Furthermore, the metabolic shift towards aerobic glycolysis leads to decreased AMPK activity, which serves as the primary energy sensing complex within the cell. This alteration in AMPK regulation leads to activation of the mTOR pathway and fatty acid synthesis, which further drives tumor development and progression.

Based on the previously described preclinical observations from our group and others, we hypothesize that combined VEFGR and EGFR blockade would inhibit critical HIF-driven downstream targets including those mediating tumor angiogenesis. Recent evidence also suggests that EGFR serves as a heterodimeric partner for SGLT1, a cell surface glucose transporter, and can thus affect cellular glucose delivery. We hypothesize that combined VEGFR/EGFR blockage will constrain glucose delivery to tumors, thus effectively limiting energy production by aerobic glycolysis. An ongoing NCI phase 2 trial of bevacizumab in combination with erlotinib (10-C-0114) was undertaken based on this premise.

Vandetanib has shown activity in several preclinical tumor models and has demonstrated an acceptable toxicity profile in phase I and phase II studies. Vandetanib has demonstrated potent activity as a single agent in preclinical models of FH -/- and SDH -/- tumors. Metformin has also been shown in preclinical models to reverse some aspects of the FH-deficient phenotype in HLRCC cells by increasing AMPK activity and inhibiting the enzymes responsible for fatty acid synthesis. In combination, vandetanib and metformin show synergistic anti-tumor activity in relevant preclinical models. This drug combination thus provides an exciting opportunity for exploring a targeted approach in a cancer with essentially no available curative options.

As part of this study, we also propose to evaluate the activity of this regimen in patients with sporadic papillary RCC, in whom there is currently no evidence of a heritable germline FH or SDH defect. As previously mentioned, there are currently no standard treatment options for patients with advanced papillary RCC. Given the relatively recent identification of Krebs cycle alterations in hereditary forms of papillary RCC, we propose to explore the possibility that some variants of sporadic papillary RCC may share common clinical/molecular features with HLRCC/SDH-associated renal tumors that may render them amenable to treatment with this regimen. As part of this trial, an attempt will be made to further characterize these sporadic tumors, particularly with regard to the prevalence of somatic FH/SDH inactivation and VEGF/EGFR pathway activation.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Diagnosis/Histology

a. Phase I Component – Histologically confirmed advanced RCC of any subtype.
b. Phase II Component – Advanced RCC associated with 1) HLRCC or SDH (Cohort 1); OR 2) advanced non HLRCC-related papillary RCC (Cohort 2).

2.1.1.2 Phase 1: Patients must have evaluable disease

Phase 2: Patients must have measurable disease based on RECIST 1.1 criteria. See Section **6.2** for the evaluation of measurable disease.

2.1.1.3 Prior Therapy

a. Phase 1- Patients with clear cell RCC must have either declined, be ineligible to receive, have progressed on, or be intolerant to high dose IL-2, or standard first and second line VEGF, or mTOR targeted agents. As there is no standard therapy for metastatic non-clear cell RCC, no prior therapy is required.
b. Phase 2- No more than two prior VEGF-pathway targeted agents
c. No previous treatment with vandetanib. Previous or ongoing treatment with metformin is allowed.

2.1.1.4 Age ≥18 years.

2.1.1.5 ECOG performance status <2 (Karnofsky >60%, see **Appendix A**).

2.1.1.6 Negative pregnancy test (urine or serum) for female patients of childbearing potential.

2.1.1.7 Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥ 1,500/mcL
- platelets ≥ 100,000/mcL
- total bilirubin ≤ 1.5x upper limit of reference range (< 3x upper limit of reference range in patients with Gilbert's disease)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal
- eGFR (CKD-EPI) ≥ 50 mL/min/1.73 m^2

2.1.1.8 Men and women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for at least 6 months after vandetanib/metformin therapy. Should a woman become pregnant (either a participant or the partner of a male participant) or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Known serious allergic reaction to vandetanib or metformin.

2.1.2.2 Brain metastases or spinal cord compression that requires treatment, unless the treatment ended at least 4 weeks before starting protocol therapy and the condition has been stable without steroid treatment for at least 10 days.

2.1.2.3 Major surgery (includes any surgery that carries significant risk of blood loss, extended periods of general anesthesia, or requires at least an overnight hospital admission) within 28 days before starting treatment or inadequately healed incision/scar from prior surgery.

2.1.2.4 Any unresolved chronic toxicity greater than Common Terminology Criteria for Adverse Event (CTCAE) Grade 2 or greater from previous anti-cancer therapy (this criterion does not apply to alopecia).

2.1.2.5 Unacceptable electrolyte values, including:

- Potassium <4.0 mmol/L despite supplementation, or elevated potassium above the CTCAE Grade 1 upper limit.
- Magnesium below the lower limit of normal range despite supplementation, or elevated magnesium above the CTCAE Grade 1 upper limit.
- Ionized calcium or corrected calcium values below the normal range or hypercalcemia above the CTCAE Grade 1 upper limit.

2.1.2.6 Significant cardiac event (e.g., myocardial infarction), New York Heart Association (NYHA) classification of heart disease ≥2 within 12 weeks before starting treatment (see **Appendix B**), or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.

2.1.2.7 History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.

2.1.2.8 Hypertension not controlled by medical therapy (systolic blood pressure greater than 140 millimeters of mercury [mmHg] or diastolic blood pressure greater than 90 mmHg).

2.1.2.9 Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.

2.1.2.10 Proteinuria > 1gram/24 hrs.

2.1.2.11 Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol.

2.1.2.12 Previous or current invasive malignancies of other histologies requiring treatment within the last 2 years, with the exception of adequately treated basal cell or squamous cell carcinoma of the skin (phase 2 only).

2.1.2.13 Congenital long QT syndrome.

2.1.2.14 Any concomitant medications that are known to be associated with Torsades de Pointes (see **Appendix C**) Drugs listed in Appendix C, **Table 3**, that in the investigator's opinion cannot be discontinued, are allowed however, must be monitored closely

2.1.2.15 Any concomitant potent inducers of cytochrome P450 3A4 (CYP3A4) function (see http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a continually updated list of CYP3A4 inducers).

2.1.2.16 History of QT prolongation associated with other medications that required discontinuation of that medication.

2.1.2.17 QTcF correction unmeasurable or >450 ms on screening ECG (Note: If a patient has a QTcF interval >450 ms on screening ECG, the screening ECG may be repeated twice [at least 24 hours apart] for a total of 3 ECGs. The average QTcF from the three screening ECGs must be ≤450 ms in order for the patient to be eligible for the study).

2.1.2.18 Women that are currently breast feeding.

2.1.2.19 Active treatment-refractory diarrhea that may affect the ability of the patient to absorb the trial agents or tolerate further diarrhea.

2.1.2.20 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with vandetanib/metformin.

2.1.2.21 Patients with active hemoptysis, clinically significant non hemorrhoidal GI bleeding or those with bleeding diathesis

2.2 SCREENING EVALUATION

The following screening studies must be performed within 4 weeks prior to enrollment on study:

- A complete history and physical with documentation of measurable disease and performance status
- Pathology confirmation of diagnosis from any certified laboratory of pathology although every effort will be made to obtain slides and confirm the diagnosis with NIH pathology department.
- 12 lead ECG
- Echocardiogram

The following must be performed within 2 weeks prior to enrollment on study:

- Imaging studies: CT of the chest abdomen and pelvis (or MRI scans when indicated)
- MRI (or CT with contrast) of the brain
- Targeted history and physical examination focusing on any salient changes from baseline
- CBC with differential, Hepatic Panel, Acute Care Panel, Mineral Panel, urinalysis, spot urine protein:creatinine ratio (patients with 1+ or greater proteinuria on UA and a spot urine protein:creatinine ratio of > 0.5 will undergo a 24 hour urine collection for quantitation of proteinuria)
- Urine or serum pregnancy test in women of childbearing potential

2.3 RECRUITMENT STRATEGIES

Patients will be recruited through clinical referrals to the UOB branch and the clinical trial will be listed on *www.clinicaltrials.gov*. Recruitment letters and other recruitment tools available to CCR investigators may also be used. Both men and women of all races are eligible for this trial.

2.4 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 sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call 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 to the research team. A recorder is available during non-working hours.

2.5 TREATMENT ASSIGNMENT PROCEDURES

Cohorts:

Number	Name	Description
1	Phase I Component	Subjects with advanced RCC enrolled to determine the MTD
2	Phase II component/Cohort I	Subjects with metastatic HLRCC/SDH associated renal cancer enrolled after the MTD has been identified
3	Phase II component/Cohort II	Subjects with sporadic/non-HLRCC papillary renal cancer enrolled after the MTD has been identified

Arms

Number	Name	Description
1	Phase I component	Vandetanib and metformin
2	Phase II component	Vandetanib and metformin

Subjects in cohort 1 will be directly assigned to arm 1. Subjects in cohort 2 and 3 will be directly assigned to arm 2.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

The phase I component is designed as a single arm, fixed order dose-escalation study of various doses of vandetanib and metformin using a modified Fibonacci schema until MTD is reached or the highest proposed dose level is tested without reaching MTD (see details below). The design for the phase II component will be an open label, single arm study utilizing a fixed starting dose

of vandetanib and metformin, which will be determined based on the MTD established by the phase I component of the study. The duration of each cycle will be 28 days.

For metformin doses above 250 mg bid there will be a lead-in period of approximately 2 weeks to help minimize GI side effects associated with this drug. Metformin will be started at a dose of 250 mg bid on Day -14 and over a course of approximately 2 weeks the agent will be titrated to the target dose. Vandetanib will also be taken starting on Day -13 during the lead in period at the assigned dose. Once the lead in period is complete and both agents are at the assigned dose level, cycle 1 will begin.

For metformin doses ≤ 250 mg bid **(**without metformin lead-in), metformin will be taken starting on Cycle 1 Day 1 and vandetanib will be taken starting on Cycle 1 Day 2.

The lead in will not be required in cases of intrapatient dose escalation.

Patients who are on metformin will have their metformin discontinued prior to study entry. Once enrolled, metformin will be dosed/titrated as appropriate for the relevant dose level.

Patients will undergo clinical and laboratory evaluation prior to the start of drug administration. While the patient's local physician outside the NIH Clinical Center may evaluate the patient for new complaints or ongoing medical issues, the patient will return to the NIH Clinical Center for formal evaluation after each cycle.

Patients will be evaluated radiologically for evidence of response or progression approximately 8 weeks after initiation of therapy, every 8 weeks thereafter for the first 32 weeks, and then every 12 weeks while on treatment. Patients with evidence of disease response or stable disease will continue to receive therapy in the absence of unacceptable toxicity.

Figure 17: Cycle 1 for metformin doses > 250 mg BID

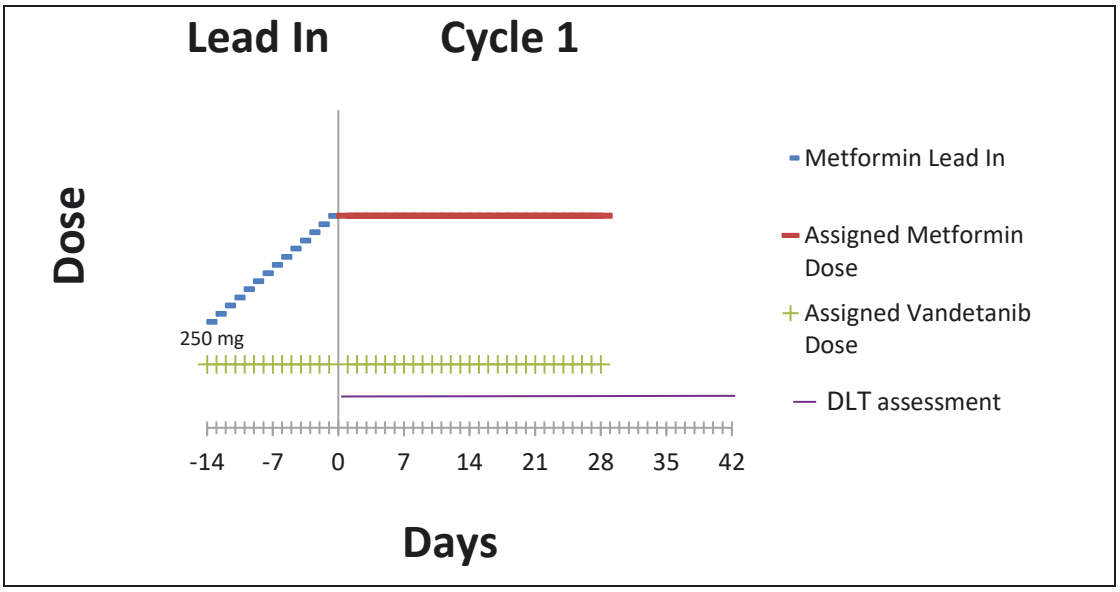
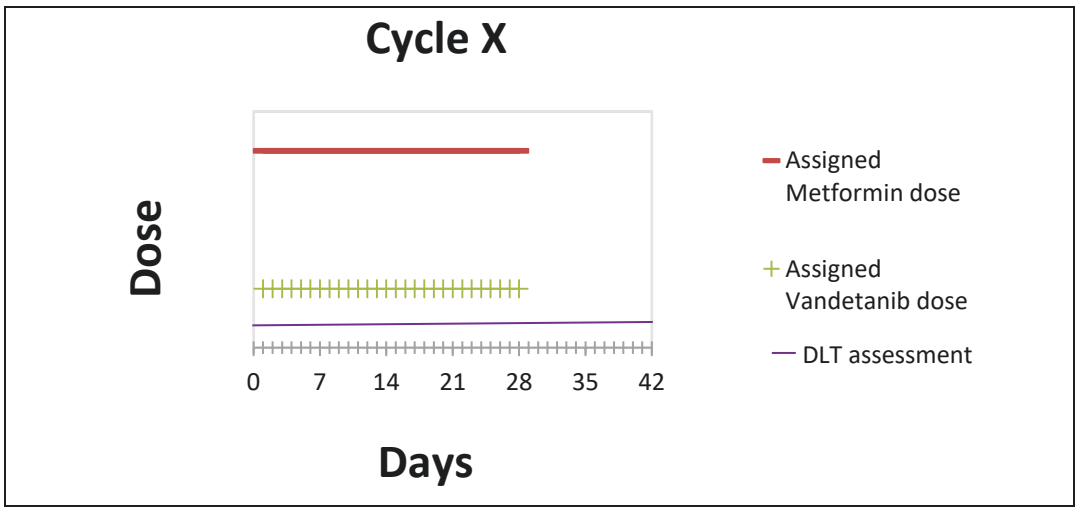


Figure 18: Cycle 1 for metformin doses ≤ 250 mg BID and Cycles 2 onward for all metformin doses



3.1.1 Phase I Component

3.1.1.1 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as an adverse event that is related (possibly, probably, or definitely) to administration of vandetanib and/or metformin. DLTs (defined as those occurring within the first 42 days of treatment after the intended dose of metformin is achieved for a given dose level; based on CTCAE Version 4.0) will include:

- grade IV or greater hematological toxicity
- neutropenic fever
- grade III or greater nonhematological toxicity with the following exceptions. For the AEs below, DLT is defined as:
    - grade III or greater diarrhea leading to hospitalization or lasting > 48 hours despite optimal anti-diarrheal medication; grade IV diarrhea despite optimal anti-diarrheal prophylaxis
    - grade III or greater nausea or vomiting despite optimal antiemetics
    - grade III hypertension that is not controlled (to 140/90 mmHg or below) despite optimal antihypertensive therapy
    - grade III elevated serum creatinine that cannot be corrected to grade 1 or better with hydration within 48 hours
    - electrolyte abnormalities that cannot be corrected with medical management within 72 hours

3.1.1.2 Dose Escalation

Dose escalation will proceed in cohorts of 3-6 patients each as outlined below. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during 1 cycle of treatment (42 days from the time the intended dose of metformin is reached for a given dose level), and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of the experimental regimen. Patients are considered evaluable for toxicity for the purpose of cohort dose escalation decisions if they either 1) experienced DLT or 2) have received at least 75% of the planned dose of treatment in one cycle of therapy and have been followed for one full cycle without DLT. All toxicities will be reported for all patients who receive any amount of study drug on this study. Additional dose levels may be considered if dose level 3 is well tolerated and will require an amendment to allow further dose escalations. Additional dose levels with serial escalation of metformin may also be considered if DLT at dose level 1 necessitates reduction in the dose of vandetanib to below 300mg as long as no more than 1/6 patients at the lower dose level experience a DLT (for instance, if <1/6 pts at dose level -1 experience DLT, one or more additional dose levels with 200mg of vandetanib and escalating doses of metformin. (250mg BID, 500mg BID etc. may be considered, via a protocol amendment. In addition, based on PK parameters ascertained from earlier dose levels, the protocol may be amended to evaluate once daily dosing of metformin in dose levels 2-4. Determination of DLT for the purposes of establishing a maximum tolerated dose (MTD) will be done taking into consideration the toxicities observed in cycle 1.

If a DLT is encountered during dose escalation of metformin in the lead-in period, it will count as a DLT at the corresponding dose level. This may require declaring a lower dose level as the MTD or accruing additional patients at that dose level before further dose escalation.

Dose escalation schedule:

The starting Dose Level (Dose Level 1) = vandetanib 300mg PO daily and metformin 250mg PO daily

Dose Level	***Vandetanib***	***Metformin***
-3	100mg every other day	250mg QD
-2	100mg daily	250mg QD
-1	200mg daily	250mg QD
1	**300mg daily**	**250mg QD**
2	300 mg daily	250 mg BID
3	300mg daily	500mg BID
4	300mg daily	850mg BID

Dose escalation will follow the rules outlined below.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level	This is the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Once three patients have been enrolled at a given dose level, no additional patients will be enrolled until evaluation for DLT is complete in those patients. If a DLT is seen in no more than one of three patients, an additional three patients will be enrolled at the dose level; no further patients will be enrolled until DLT evaluation in the additional patients is complete.

3.1.1.3 Intra-patient dose modifications

Dose-Escalation: Intra-patient dose escalation may be allowed at the discretion of the principal investigator if the following conditions are met: a) the patient has not experienced drug-related toxicity > grade 2 after one course of study treatment at the initial dose level; b) the higher dose level has been completed by all patients in that cohort and no more than 1/6 patients experienced a DLT, and c) there is no evidence of disease progression as defined by RECIST. If patients experience DLT at the higher dose level, dose modifications will be made as outlined in sections **3.3.3** and **3.3.4**. Once the MTD has been established that will serve as the ceiling and apply to every patient thereafter. That is, intra-patient dose escalations will not exceed the established MTD.

Dose-Reduction: Patients who experience DLTs (during the first or subsequent cycles of therapy), may be allowed to continue on study with dose reductions if there is a prospect of benefit from continuing therapy. The agent to be dose-reduced and the dose levels to be used are outlined in sections **3.3.3** and **3.3.4**.

3.2 DRUG ADMINISTRATION

The duration of each cycle will be 28 days. For metformin doses above 250 mg bid there will be a lead-in period of approximately 2 weeks to help minimize GI side effects associated with metformin. Metformin will be started at a dose of 250 mg bid on Day -14 and over a course of approximately 2 weeks the agent will be titrated to the target dose. Vandetanib will also be taken starting on Day -13 during the lead in period at the assigned dose. Once the lead in period is complete and both agents are at the assigned dose level, cycle 1 will begin. For metformin doses ≤ 250 mg bid **(**without metformin lead-in), metformin will be taken starting on Cycle 1 Day 1 and vandetanib will be taken starting on Cycle 1 Day 2. If a DLT is encountered during dose escalation of metformin in the lead-in period, it will count as a DLT at the corresponding dose level. This may require declaring a lower dose level as the MTD or accruing additional patients at that dose level before further dose escalation.

The study drugs will be dispensed by the NIH pharmacy and will be given to the subjects for daily self-administration with detailed instructions. For the phase I component of the study, the dose of each agent will depend on the dose level at which the subject is enrolled. The dose for the phase II component will be determined following completion of the phase I component of the study.

Vandetanib and metformin will be administered on an outpatient basis and the drugs will be self-administered by the patient. The prescribed dose of the drugs will be taken orally and should be taken with some food and water to help minimize GI effects. Vandetanib tablets should be taken whole or dispersed in water, without crushing. If vandetanib cannot be taken whole, the tablets can be dispersed in a glass containing approximately 60 mL of non-carbonated water and stirred for approximately 10 minutes until the tablets are dispersed (will not completely dissolve). No other liquids should be used. The mixture should be swallowed immediately. To ensure the full dose is received, the patient should refill the glass with an additional half glass of water and mix with any remaining drug and drink it. If the subject inadvertently does not take the dose in the morning, he or she may take that day's dose any time up to10 p.m. 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.

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.

Patients will be required to maintain a diary (see **Appendix D**) documenting when the doses of vandetanib and metformin were taken and any associated side effects.

3.3 TREATMENT MODIFICATIONS

3.3.1 General Plan to Manage Safety

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section **2.1.2**) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before enrollment on trial and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, daily blood pressure monitoring, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study will be evaluated approximately 60 days after the decision to discontinue treatment as outlined in section **3.6**. The safety monitoring is incorporated into the study calendar in section **3.5**.

Hypertension will be monitored through routine evaluation of blood pressure at each clinic visit, as well as by patient self-monitoring. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without vandetanib/metformin.

Renal function will be monitored by serum creatinine measurement. Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick.

If patients on treatment with vandetanib require elective major surgery, it is recommended that vandetanib be held for 4 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart vandetanib until 4 weeks after that procedure and/or adequate wound healing has occurred (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks after surgery**).** Patients can continue taking metformin until the day before surgery and can resume following surgery as long as they maintain a creatinine clearance/eGFR of ≥ 50 ml/min and have resumed normal p.o. intake.

Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: alcohol-free emollient cream, diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended.

Both vandetanib and metformin can cause diarrhea. Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and vandetanib/metformin dose reduction/interruption as described in Sections **3.3.3** and **3.3.4**. These symptoms will be self-reported and inquiries will be made at clinic visits, also outlined in the study calendar in section **3.5**.

Liver function abnormalities, including elevated serum ALT, AST, and/or alkaline phosphatase, have been observed with single-agent vandetanib. Periodic monitoring of liver function will be performed on study. Vandetanib dosing should be interrupted if changes in liver function are severe (as outlined in section **3.3.3**).

While lactic acidosis is a rare metabolic complication that can occur due to metformin accumulation, serum lactate will be evaluated periodically and dose reduction/interruption will proceed as described in Section **3.3.4**.

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients will be warned against excessive alcohol intake, acute or chronic, while receiving metformin.

Decrease in vitamin B12 levels can occur infrequently with chronic metformin use. Hematologic parameters that are consistent with vitamin B12 deficiency (i.e. megaloblastic anemia) should be appropriately investigated. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2- to 3-year intervals is recommended by the manufacturer.

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

3.3.2 Dose Modifications

Patients will be asked to record side effects/symptoms developing or worsening on therapy on a Side Effect Diary (see **Appendix D**) 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 4.0) related to either vandetanib or metformin according to the guidelines below. For grade 1 and 2 adverse events (AEs) related to the investigational agents, one or both agents may be held if the AE is determined to be intolerable. Agents may be restarted at the same dose or one dose level lower once the AE improves. Dose modifications for laboratory abnormalities will be required only if these abnormalities are clinically significant (regardless of grade). There will be no dose modifications for electrolyte abnormalities (potassium, sodium, calcium, magnesium, phosphorus) that can be corrected (to $\leq$ grade 1 or baseline) within 72 hours. In the event metformin is discontinued permanently, the patient can continue to receive vandetanib in the absence of an indication requiring permanent discontinuation of that agent.

3.3.3 Dose Modifications for Toxicities Related to Vandetanib

The following dose levels will be used to guide reductions in vandetanib dosage:

Current Dose	Reduce to
300 mg po qd	200 mg po qd
200 mg po qd	100 mg po qd
100 mg po qd	100 mg po qod

Any permanent discontinuation of vandetanib will also result in a permanent discontinuation of metformin.

3.3.3.1 Cardiac toxicity - QTc prolongation

Electrocardiograms will be evaluated by suitably qualified personnel for the presence of QTc (using Fridericia's correction; the term QTc will refer to QTc calculated by this method unless otherwise specified) prolongation or other abnormalities, in particular, any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia. Any clinically significant abnormal findings or QTc prolongations will be recorded as AEs. The schedule of monitoring is provided in the study calendar in section **3.5**.

In addition to scheduled ECG, additional ECGs should also be performed in the event of QTc prolongation, both during and post the prolongation period.

- During the QTc prolongation period: For a single QTc value of >500 ms, vandetanib must be withheld. Electrocardiograms will be followed at least once per week (done on the same day each week +/- 2 days) along with electrolytes, until QTc falls ≤450 ms. Vandetanib treatment may be resumed at a permanently lower dose (reduced one dose level as outlined above) after the QTc returns to ≤450 ms.

- Post the QTc prolongation period: If vandetanib (at the reduced dose) is restarted after the QTc prolongation has resolved, ECGs and electrolytes (including calcium and magnesium) must be obtained at 3, 8, and 12 weeks following the start of the lower dose. Serum potassium levels should be maintained at 4 mEq/L or higher, and serum magnesium and serum calcium should be kept within normal range to reduce the risk of QT prolongation and torsades. ECG and electrolyte monitoring can then resume every 4 weeks at the normal visit schedule for the patient.

- If a patient is on 100 mg vandetanib dose and has QTc >500 ms, vandetanib must be permanently discontinued.

3.3.3.2 Gastrointestinal toxicity

Nausea, vomiting, or both may be controlled with anti-emetic therapy. The use of somatostatin or a somatostatin analogue is allowed to control diarrhea. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. No dose modifications will be

made for Grade 1 or 2 diarrhea; however, electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation. If CTCAE Grade 3 nausea or vomiting develops despite optimal prophylaxis/treatment, vandetanib should be withheld until resolution to CTCAE Grade 1 or baseline; vandetanib can then be restarted at a permanently reduced dose (reduced one dose level).

If CTCAE Grade 3 diarrhea develops despite optimal prophylaxis/treatment, vandetanib should be withheld until diarrhea resolves to CTCAE Grade 1 or baseline; vandetanib can then be restarted at a permanently reduced dose (reduced one dose level). Any electrolyte imbalance must be promptly corrected since hypokalemia and hypomagnesemia are potential risk factors for drug-induced arrhythmia.

Vandetanib will be permanently discontinued in the event of grade 4 nausea, vomiting or diarrhea occurring despite optimal prophylaxis/treatment.

3.3.3.3 Cutaneous toxicity

It is strongly recommended that all patients follow a program of sun protective measures (wearing additional clothing and/or sunscreen) while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. The aim is to reduce the risk of development of skin rash, or 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 following actions are recommended to the Investigator for the management of this reaction:

- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams or systemic glucocorticoids, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

- The rash should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria.

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

- If a rash of CTCAE Grade 3 is detected, vandetanib should be withheld until recovery to CTCAE Grade 1 or baseline; vandetanib can then be restarted at a permanently reduced dose (reduced one dose level as outlined above).

- Vandetanib will be permanently discontinued if grade 4 rash related to the agent develops

3.3.3.4 Hypertension

Hypertension is one of the most common toxicities experienced with vandetanib. Subjects will be asked to monitor their blood pressure at home at least once a day and contact the UOB team for elevated readings. Elevated BP readings should be confirmed by a qualified health care

professional when possible and decisions regarding grading of hypertension and initiation/intensification of antihypertensive therapy will generally be driven by BP measurements performed by a health care professional.

Table 1 outlines the management plan for patients developing hypertension on therapy. Although the active version of CTCAE criteria will be used to grade hypertension, the scheme outlined in the table below 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.

The choice of agents and dosage used may vary based on individual circumstances. Calcium channel blockers, beta blockers, diuretics, ACE inhibitors, and angiotensin receptor blockers are examples of classes of antihypertensive agents that may be used.

Table 1: Hypertension will be managed in accordance with the guidelines outlined in the table below:

	BP Measurements - Systolic/Diastolic	**Treatment/Dose Modification**
A	>140 mmHg (systolic) OR >90 mmHg (diastolic) OR Increase of diastolic BP by ≥20 mmHg over baseline BP	• Add new or additional antihypertensive medications or increase dose of existing medications. • Maintain dose of vandetanib and metformin. • If unable to control BP to <140/90 in two weeks, hold vandetanib and follow guidelines under row C
B	>160 mmHg (systolic) OR >100 mmHg (diastolic) OR Symptomatic	• Hold vandetanib. • Add new or additional antihypertensive medications or increase dose of existing medications. • Resume treatment at same dose level when BP falls to <140/90 or baseline.
C	>140 mmHg (systolic) OR >90 mmHg (diastolic) Despite therapy for at least 2 weeks	• Hold vandetanib. • Maintain or intensify antihypertensive therapy • Resume treatment at same dose level when BP falls to <140/90 or baseline
D	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	• Discontinue vandetanib • No further treatment with vandetanib allowed except in patients benefiting from therapy in whom treatment may be restarted if BP is controlled to <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

3.3.3.5 Pulmonary toxicity

Although relatively rare, ILD associated with EGFR inhibitors, including vandetanib can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, vandetanib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often used. Vandetanib should not be restarted in those patients with drug-related ILD.

3.3.3.6 Other toxicity

Patients who experience any other CTCAE (version 4) Grade 3 toxicity that is considered related to vandetanib will have their study drug temporarily stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE Grade 1 (or baseline) the patient may restart treatment at a permanently reduced dose (reduced one dose level as outlined above). Vandetanib will be permanently discontinued in patients who develop grade 4 toxicities thought to be related to the agent. All SAEs and study drug-related AEs must be followed until resolution to grade 1 or less/baseline unless in the Investigator's opinion, the event has stabilized or is unlikely to resolve due to the patient's underlying condition or other factors.

If the patient has been off treatment for greater than 6 weeks due to toxicity, he/she must be withdrawn from vandetanib.

3.3.4 Dose Modifications for Toxicities Related to Metformin

The following dose levels will be used to guide reductions in metformin dosage:

Current Dose	Reduce to
850 mg po bid	500 mg po bid
500 mg po bid	250 mg po bid

3.3.4.1 Gastrointestinal toxicity

Both vandetanib and metformin can cause gastrointestinal issues, particularly diarrhea. Nausea, vomiting, or both may be controlled with anti-emetic therapy. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. No dose modifications will be made for Grade 1 or 2 diarrhea, however, electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation.

If CTCAE Grade 3 diarrhea develops, metformin should be withheld until diarrhea resolves to CTCAE Grade 1 or baseline. If metformin is thought to be causative (typically occurs within the first few weeks of therapy), it can then be restarted at a reduced dose as outlined in the dose modification scheme in this section (above). Metformin will be discontinued permanently in the

event of grade 4 diarrhea related to the agent. Any electrolyte imbalance must be promptly corrected since hypokalemia and hypomagnesemia are potential risk factors for drug-induced arrhythmia.

3.3.4.2 Lactic acidosis

Patients taking metformin can rarely develop lactic acidosis. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis may be used to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

If lactic acidosis develops, it will be assumed to be due to metformin and the study drug will be permanently stopped. Since vandetanib has been associated with impaired renal function (potentially exacerbating lactic acidosis) and since acidosis might lead to electrolyte disturbances that can potentiate vandetanib-associated cardiac toxicity, vandetanib will be held in patients with lactic acidosis until resolution of the event but can be resumed thereafter at the previous dose level.

3.3.4.3 Other toxicity

Patients who experience a CTCAE (version 4) Grade 3 toxicity that is considered related to metformin will have their study drug temporarily stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE Grade 1 (or baseline) the patient may restart treatment at a permanently reduced dose (reduced one dose level as outlined above).

The Investigator can reduce the dose of metformin to the lowest dose of 250 mg BID. If a patient experiences a Grade 3 or 4 toxicity that is considered related to metformin while on the 250 mg dose, they will have study drug permanently stopped.

Metformin will be withheld under the following circumstances, regardless of whether these events are related to the agent:

1) Although metformin is not associated with renal impairment, patients with impaired renal function are at higher risk for lactic acidosis. Therefore, metformin should be temporarily discontinued in all patients with an eGFR of 40 ml/min or less regardless of causality. Metformin can be restarted at the previous dose once the eGFR improves to 50 ml/min or higher.
2) The risk of lactic acidosis from metformin may be increased in patients with hepatic dysfunction. Therefore, patients with grade 3 or higher AST/ALT elevations or hyperbilirubinemia will have their metformin held until these values return to grade 1/baseline.
3) Patients receiving iodinated IV contrast agents (for CT scans etc.) will have their metformin held on the morning of the planned procedure. A serum creatinine/eGFR will be rechecked approximately 2 days after the procedure and metformin may be restarted if the eGFR is >40 ml/min.

All SAEs and study drug-related AEs must be followed until resolution to grade 1 or less/baseline unless in the Investigator's opinion, the event has stabilized or is unlikely to resolve due to the patient's underlying condition or other factors.

If the patient has been off treatment for greater than 6 weeks due to toxicity, he/she must be withdrawn from metformin.

3.3.5 Treatment interruptions unrelated to toxicity

Surgery

Major elective surgical procedures should not be scheduled during protocol treatment or within 4 weeks of the last dose of vandetanib. Patients undergoing unexpected major surgical procedures should have the study agents withheld. Treatment may be resumed at a later date at the discretion of the PI (vandetanib should not be resumed earlier than 4 weeks post-operatively, with adequately healed incisions). Patients requiring surgical resection of one or more of their metastatic lesions will discontinue treatment permanently.

Radiation

Patients requiring radiation therapy for RCC will permanently discontinue study treatment.

3.3.6 Management of Female Study Subjects

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with vandetanib/metformin and should use adequate contraception during and for at least 6 months after vandetanib/metformin therapy as indicated in section **2.1.1.8**. Women who become pregnant while on vandetanib/metformin will discontinue the drug combination. It is not known whether vandetanib is excreted in human milk. Low amounts of metformin (generally ≤1% of the weight-adjusted maternal dose) are excreted into breast milk. Women will not be permitted to breast-feed while receiving vandetanib/metformin therapy.

3.4 STUDY EVALUATION

3.4.1 Baseline Evaluation

Baseline studies need not be repeated if they have been performed within the timeframes listed below at screening.

The following baseline studies must be performed within 4 weeks prior to enrollment on study:

- A complete history and physical with documentation of measurable disease and performance status
- 12 lead ECG
- Photographic evaluation of skin leiomyoma (only in patients with HLRCC associated cutaneous leiomyomas)

The following must be performed within 2 weeks prior to enrollment on study:

- Imaging studies: CT of the chest abdomen and pelvis (or MRI scans when indicated)
- MRI (or CT with contrast) of the brain
- PET scan
- Bone Scan
- Targeted history and physical examination focusing on any salient changes from baseline
- CBC with differential, Acute Care Panel, Hepatic Panel, Mineral Panel, LDH, total protein, creatine kinase, uric acid, PT/PTT, urinalysis, spot urine protein:creatinine ratio (patients with 1+ or greater proteinuria on UA and a spot urine protein:creatinine ratio of > 0.5 will undergo a 24 hour urine collection for quantitation of proteinuria)
- Urine or serum pregnancy test in women of childbearing potential
- TSH, T3 and T4 tests

3.4.2 Each cycle

All patients must be seen at NIH Clinical Center at the beginning of each cycle. Interim assessments may be performed by a local laboratory/physician. For patients requiring a metformin lead-in, a visit to the NIH Clinical Center will also be required on Day 15 of Cycle 2. See **Study Calendar** for labs done if C2D15 if required.

Assessments may be performed within ± 7 days of what is indicated with exception of ECG.

- Limited history and physical focusing on relevant changes from initial H&P (performed on days 15 and 28 in cycle 1 and on day 28 of subsequent cycles)
- CBC, Hepatic Panel, LDH, total protein, creatine kinase, uric acid, urinalysis, spot urine protein:creatinine ratio (performed on days 15 and 28 in cycle 1 and on day 28 of subsequent cycles)
- Acute Care Panel, Mineral Panel, lactate (performed weekly in cycle 1 & days 15 and 28 in cycle 2, then on day 28 of subsequent cycles)
- Pregnancy test in women of childbearing potential
- 12-lead ECG within 4-8 hours after first dose of vandetanib on day -13 for metformin lead-in patients and cycle 1 day 2 for patients without metformin lead-in, then weekly during the first cycle & days 15 and 28 in cycle 2, then on day 28 of subsequent cycles)
- Research PET scan on Cycle 1 Day 15, if positive at baseline
- TSH, T3 and T4 tests at 2-4 weeks, 8-12 weeks, and then every 3 months thereafter.

3.4.3 Restaging cycles

Every two cycles (every 8 weeks) during first 8 cycles (first 32 weeks), then every three cycles (every 12 weeks) thereafter

- Imaging studies: CT/MRI evaluation of known/suspected disease sites, bone scan (if positive for metastatic bony disease at baseline)
- PET scan (only when necessary to supplement CT/MRI, for instance new lesions of uncertain etiology, to confirm CR etc.)
- Dermatology Consult with photographic evaluation of skin leiomyoma (only in patients with HLRCC associated cutaneous leiomyomas)

3.4.4 Daily Monitoring

Blood Pressure- Patient will be asked to measure and record his/her blood pressure at least once a day and will be provided with an automated/semi-automated BP monitor. Patients will be instructed to record BP readings on a BP monitoring diary which will be provided (see **Appendix F**) 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 140/90 mmHg and may be instructed to have elevated readings confirmed by a local health care provider.

3.5 STUDY CALENDAR

All patients must be seen at NIH Clinical Center at the beginning of each cycle. Interim assessments may be performed by a local laboratory/physician.

Post baseline assessments may be performed within ± 7 days of what is indicated with exception of Day -13 (metformin lead-in)/C1D2 (without metformin lead-in) ECG which must be performed 4 – 8 hours after first dose of vandetanib.

Study Drug Administration

For patients receiving >250 mg metformin (with metformin lead-in)

Study Drug	**Lead In Period**			**Cycle 1**	**Subsequent Cycles**
	Day -14	*Day -13*	*through Day -1*	*Day 1 to Day 28*	*Day 1 to Day 28*
Metformin	X →	→	→	→	→
Vandetanib		X →	→	→	→

For patients receiving ≤ 250 mg metformin (without metformin lead-in)

Study Drug	**Cycle 1**			**Subsequent Cycles**
	Day 1	*Day 2*	*through Day 28*	*Day 1 to Day 28*
Metformin	X →	→	→	→
Vandetanib		X →	→	→

Procedure[8]	**Screening[1]**	**Baseline[1]**	**Lead-in Period**	**Cycle 1**					**Cycle 2**					**Subsequent Cycles**	**60 Day Safety Visit**	**Long Term Follow Up[7]**
				Day 1	**Day 7**	**Day 15**	**Day 21**	**Day 28**	**Day 1 (day 29 of previous cycle)**	**Day 7**	**Day 15**	**Day 21**	**Day 28**	**Day 28**		
History and PE	X	X				X		X			X[2]		X	X	X	
Vital signs	X	X				X		X			X[2]		X	X	X	
Performance Score	X	X														
Acute Care Panel, Mineral Panel, lactate	X	X			X	X	X	X		X	X	X	X	X	X	
CBC, Hepatic Panel, urinalysis, UPCR	X	X				X		X			X[2]		X	X	X[5]	
LDH, total protein, creatine kinase, uric acid, PT/PTT	X	X				X		X			X[2]		X	X		
Serum or urine βHCG in women of child bearing potential only	X	X						X					X	X		
TSH, T3 and T4		X				2-4 weeks							8-12 weeks and every 3 months thereafter			

Procedure[8]	**Screening[1]**	**Baseline[1]**	**Lead-in Period**	**Cycle 1**					**Cycle 2**					**Subsequent Cycles**	**60 Day Safety Visit**	**Long Term Follow Up[7]**
				Day 1	**Day 7**	**Day 15**	**Day 21**	**Day 28**	**Day 1 (day 29 of previous cycle)**	**Day 7**	**Day 15**	**Day 21**	**Day 28**	**Day 28**		
Pathology Confirmation of Diagnosis	X															
CT chest (and neck, if indicated) + CT or MRI abdomen/pelvis[9]	X	X							Every 2 cycles during the first 8 cycles, then every 3 cycles thereafter							
Brain MRI or CT with contrast	X	X														
Bone Scan[9]		X							If positive at baseline, every 2 cycles during the first 8 cycles, then every 3 cycles thereafter							
PET/CT scan[9]		X				X[10]								X[10]		
Photographic evaluation of skin leiomyoma[4, 9]		X							Every 2 cycles during the first 8 cycles, then every 3 cycles thereafter							
Echocardiogram	X															
ECG	X	X	X[3]	X[3]		X	X	X	X		X	X	X	X	X		
Pharmacokinetic Studies			X[11]	X[12]					X[13]							
Pharmacogenetic Studies		X														

Procedure[8]	Screening[1]	Baseline[1]	Lead-in Period	Cycle 1					Cycle 2					Subsequent Cycles	60 Day Safety Visit	Long Term Follow Up[7]
				Day 1	Day 7	Day 15	Day 21	Day 28	Day 1 (day 29 of previous cycle)	Day 7	Day 15	Day 21	Day 28	Day 28		
Optional biopsy of accessible tumor		X										X				
Correlative Research Studies[7]		X		At the end of every other cycle through cycle 8 and at the time of disease progression												
Adverse Events		X	→	→	→	→	→	→	→	→	→	→	→			
Concomitant Medications		X	→	→	→	→	→	→	→	→	→	→	→			
Blood pressure monitoring				Performed daily by patient												
Annual phone calls																X

[1] Baseline studies do not need to be repeated if already performed at appropriate time during screening. See sections **2.2** and **3.4.1** for timing of screening and baseline studies.

[2] Only required in patients that have had a metformin lead-in.

[3] Performed within 4 to 8 hours after first dose of vandetanib on day -13 for metformin lead-in patients and cycle 1 day 2 for patients without metformin lead-in

[4] Done only in patients with HLRCC associated cutaneous leiomyomas

[5] Only ALT, AST, total and direct bilirubin should be performed at safety visit

[6] Subjects will be contacted annually for an update and to determine survival status. Any scans performed outside of NIH will be obtained when possible.

[7] 5 – 10 ml of venous blood in sodium citrate CPT tubes collected at baseline, then at the end of every other cycle through cycle 8, then at the time of disease progression; See section **5.1.2** for assessments performed on these samples.

[8]All laboratory studies will be performed within +/-5 days of the day indicated, imaging studies, optional biopsies and collection of samples for correlative studies will be performed within +/- 7 days of the indicated timepoint and ECGs within +/- 2 days of the indicated time points

[9] Restaging studies may be performed outside the indicated time period if necessitated by circumstances beyond the control of the investigators/research team.

[10] Cycle 1 Day 15 (+/- 7 days) research PET scan, if positive at baseline. Follow-up PET scan only when necessary to supplement CT/MRI.

[11] On day -14 for patients receiving >250 mg metformin (with metformin lead-in) – at pre-dose, 0.5 (+/-10 minutes), 1 (+/-10 minutes), 2 (+/-10 minutes), 3 (+/-30 minutes), 4 (+/-30 minutes), 8 (+/-30 minutes), 12 (+/-30 minutes), 18 (+/-30 minutes), and 24 (+/-30 minutes) hr post-dose.

[12] On cycle 1 day 1 for patients receiving $\leq$ 250 mg metformin (without metformin lead-in) – at pre-dose, 0.5 (+/-10 minutes), 1 (+/-10 minutes), 2 (+/-10 minutes), 3 (+/-30 minutes), 4 (+/-30 minutes), 8 (+/-30 minutes), 12 (+/-30 minutes), 18 (+/-30 minutes), and 24 (+/-30 minutes) hr post-dose.

[13] After dose titration (if necessary) – at pre-dose, 0.5 (+/-10 minutes), 1 (+/-10 minutes), 2 (+/-10 minutes), 3 (+/-30 minutes), 4 (+/-30 minutes), 8 (+/-30 minutes), 12 (+/-30 minutes), 18 (+/-30 minutes), and 24 (+/-30 minutes) hr post-dose.

3.6 FOLLOW UP EVALUATIONS

After subjects have stopped taking the study medication for any of the reasons listed in section **3.7.1** they will be seen at NIH, if feasible, for a safety visit within approximately 60 days of drug discontinuation. The safety assessments may be performed by a local physician and laboratory if patients unable to return to the NIH Clinical Center at this time or the patient may be contacted by phone for a status assessment.

The following assessments will be performed at follow up if feasible.

- History and Physical Examination
- CBC with differential, acute care panel, AST, ALT, Total and Direct Bilirubin

After the safety visit, if there are no unresolved grade 3 or higher AEs, we may, when feasible contact the patient annually by telephone to find out how they are doing and to determine survival status. If there are unresolved grade 3 – 4 AEs, patients will be followed either at the NIH Clinical Center or by their local physician. In the latter case, we will obtain the physician's record of AEs.

Any scans performed outside of the NIH will also be obtained when possible.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 60 days following the last dose of study therapy.

3.7.1 Criteria for removal from protocol therapy

- Progressive disease
- Patient is off vandetanib treatment for > 6 weeks due to toxicity
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in sections **3.3.3** and **3.3.4**
- Requires radiation or surgery for RCC
- Investigator discretion
- Positive pregnancy test

3.7.2 Off-Study Criteria

- Patient lost to follow-up
- Investigator discretion
- Participant requests to be withdrawn from study
- Death

3.7.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be

completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITTANT MEDICATION

4.1 CONCURRENT AND EXCLUDED THERAPIES

At screening, all prior anti-cancer therapy and administration of all other concomitant medication in use on the day of enrolment (signature of the ICF) will be recorded. All concomitant medications that the patient has been taking since the time of the last visit, medications the patient started between visits and all new medications will be recorded at each visit until the patient is permanently removed from study therapy. If a patient discontinues the trial agents before the final analysis, all medications including any medications started within the 60 days after the last dose, will be recorded at the appropriate discontinuation visit and the 60-day follow-up visit.

4.1.1 Prohibited medication

Patients are not eligible to enter the study if they are on any of the medication specified in the exclusion criteria.

4.1.2 Treatment for cancer

While the patient remains on study treatment, patients must not be given any concurrent cancer therapy, including cytotoxic agents, radiotherapy, biological response modifiers (including cytokines), hormonal therapy (used specifically for cancer treatment), or any other investigational agents. Bisphosphonates or other agents designed to minimize the risk of skeletal complications, such as denosumab, may be used.

4.1.3 CYP3A4 inducers

Concomitant use of known potent inducers of CYP3A4 (eg. rifampicin, phenytoin, carbamazepine, barbiturates, and St. John's Wort) are not allowed; in subjects who have discontinued use of these drugs, at least five half-lives of the drug must have elapsed before the first scheduled dose of vandetanib. Please see http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a continually updated list of CYP3A4 inducers.

4.1.4 Medication known to prolong QT interval and/or induce Torsades de Pointes

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see **Appendix C**) are not allowed during study; in subjects who have discontinued use of these drugs, at least five half-lives of the drug must have elapsed before the first scheduled dose of vandetanib (at least 4 weeks prior for levomethadyl). It is also recommended that these drugs be avoided for at least 4 weeks following discontinuation of study treatment.

4.1.5 Restricted medication

All medications prohibited in this study as indicated in **Appendix C** and in the eligibility criteria in section **2.1** must have been withdrawn for a period equivalent to at least five half-lives of the drug before the first scheduled dose of vandetanib, and should be avoided for at least 4 weeks following discontinuation of study treatment.

Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see Appendix C, **Table 3**) should be avoided during the study; in subjects who have discontinued use of these drugs, at least five half-lives of the drug must have elapsed before the first scheduled dose of vandetanib. However, these drugs will be allowed, 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. The electrolytes should be maintained within the normal range using supplements if necessary.

Warfarin is allowed in therapeutic and low-doses and these patients should be monitored regularly for changes in their International Normalized Ratio, at the discretion of the Investigator.

4.1.6 Other concomitant treatment

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. While the interaction is theoretical and not well-studied, these agents should be avoided if alternatives exist while patients are taking metformin.

4.2 SUPPORTIVE CARE

Other medication that is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator. Supportive care measures and symptomatic treatment for any treatment-associated toxicity may be instituted once the first signs of toxicity occur. Supportive care will be provided in accordance with good medical practice.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Tumor Biopsy (Optional)

Although the genes for HLRCC and SDH-related RCC are known, the genetic and biochemical abnormalities underlying the majority of papillary tumors remains unclear. Recent data (40) suggests that components of the KEAP1/NRF2 pathway may be altered in some papillary tumors, but need further study. Additionally, there are currently no prognostic biomarkers or markers that predict response of papillary tumors to therapy. Targeted sequencing and immunohistochemical studies may be performed on available tumor tissues to identify somatic genetic alterations and explore potential biomarkers. Tumor biopsies may also be used to determine the effect of therapy on VEGFR, EGFR, abl, cAMPK/mTOR and other relevant pathways that may be impacted by therapy with the combination of vandetanib/metformin.

Tumor biopsies (renal primary or metastases or cutaneous/uterine leiomyomas) may be obtained from patients who have easily accessible lesions. Core or excisional biopsy of an easily accessible sentinel lesion (such as cutaneous/subcutaneous lesions, percutaneously accessible hepatic lesions, lymph nodes etc.) may be performed at study entry and again at approximately 8 weeks following initiation of therapy. No more than 4 cores may be obtained from a single site. Biopsies that are to be used solely for research purposes will be obtained only if they can be performed with minimal risk of complications from the procedure and only after the procedure has been explained to the patient and informed consent obtained. Major surgical procedures such as laparotomy or laparoscopic procedures will not be performed solely to obtain biopsies for research purposes. The

biopsies will be performed by members of the interventional radiology, dermatology or surgical staff. A portion of the biopsies may be frozen in liquid nitrogen immediately and transferred to the UOB laboratory (Contact for receiving and processing specimen: Robert Worell/ Cathy Vocke, Ph.D. - Tel: 301-496-6353). Prior to freezing and depending on tissue availability, a small portion of the biopsy specimen may be transferred under sterile conditions to the UOB laboratory to be used to establish a tumor cell line.

In addition, attempts will be made to obtain any available archived tumor tissue on all patients to help evaluate FH and SDH status, the activation of or mutations in the NRF2/KEAP1/CUL3 pathway and/or relevant components of the VEGF/EGFR pathways. Either sequencing of individual genes or next gen sequencing as part of a limited gene panel (such as the one used by the Genetics Branch, CCR, NCI), will be used to identify the presence/absence of these somatic mutations.

Samples will be processed for the following planned studies. In the event of limited sample availability, we plan to prioritize studies in the order listed below:

- Analysis of somatic FH/SDH mutation, KEAP1, NRF2, Cul 3 and Sirt 1 mutations and IHC for markers indicating activation of the NRF2 pathway (such as NQ01) to attempt to correlate clinical effects of vandetanib and metformin with molecular abnormalities (may be performed on archived tumor tissue or tumor biopsies when available)
- Analysis of relevant pathways such as AMPK and Abl at baseline and/or modulation of these pathways in response to therapy; techniques such as IHC, Western blotting etc. may be used.
- Evaluation of HIF expression, EGFR expression, VEGFR2 expression and relevant downstream pathways; evaluation of components of the EGF and VEGF pathways may be performed to explore the correlation between these biomarkers and clinical response.
- Analysis by RT- PCR and/or IHC of transcriptional targets affected by AMPK, EGFR, and VEGF signaling pathways, including p27 KIP1, E-cadherin, b-catenin, ACC etc.
- cDNA arrays to compare gene expression profiles in tumor cells before and during treatment with vandetanib and metformin

5.1.2 Blood Samples

Collection of blood samples for research analysis may be obtained at periodic intervals which meet the NIH Guidelines for Blood Draw Limit (MAS - M95-9). No more than 10.5 mL/kg or over 550mL will be obtained from adults over an eight week period of time.

- Blood samples for evaluation of basal plasma levels of angiogenesis biomarkers including VEGF and soluble VEGFR2 and to assess the effect of vandetanib and metformin on these biomarkers. These will be obtained prior to first dose, at 8, 16, 24 and 32 weeks, and at the time of disease progression. 5-10 cc of venous blood will be collected into CPT tubes containing sodium citrate and thoroughly mixed and then transferred to the UOB laboratories for further processing and storage.

5.1.2.1 Correlative laboratory studies will be performed by investigators in the Urologic Oncology Branch (under the direction of Drs. Srinivasan, Linehan, Bottaro, Neckers) and may involve collaboration with other NIH intramural investigators including Jane Trepel.

Studies listed will be performed wherever possible and as permitted or dictated by clinical outcome and/or sample and resource availability.

5.1.3 Collection, Storage, Use and Disposition of Human Specimens

5.1.3.1 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.

5.1.3.2 Storage and research use of research human specimens

- 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 **5.1.2**).
- 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 secure UOB 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 or in the laboratories of collaborators.
- Timeframe 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.

5.2 PHARMACOKINETIC/PHARMACOGENETIC STUDIES

5.2.1 Pharmacokinetic Studies

To identify a drug interaction between metformin and vandetanib on clinically-relevant doses, blood samples for the determination of metformin plasma concentrations will be obtained from

each patient either on day -14 (day 1 of lead in period for patients receiving >250 mg metformin) or cycle 1, day 1 (for patients receiving ≤ 250 mg metformin), when metformin will be administered alone. Blood will be collected into a 6mL sodium heparin tube (BD, Franklin Lakes, NJ) at the following time points: pre-dose, 0.5 (+/-10 minutes), 1 (+/-10 minutes), 2 (+/-10 minutes), 3 (+/-30 minutes), 4 (+/-30 minutes), 8 (+/-30 minutes), 12 (+/-30 minutes), 18 (+/-30 minutes), and 24 hr (+/-30 minutes) post-dose.

After dose titration (if necessary), patients will have blood drawn at pre-dose, 0.5 (+/-10 minutes), 1 (+/-10 minutes), 2 (+/-10 minutes), 3 (+/-30 minutes), 4 (+/-30 minutes), 8 (+/-30 minutes), 12 (+/-30 minutes), 18 (+/-30 minutes), and 24 hr (+/-30 minutes) post-dose on cycle 2, day 1, after being on the daily combination of metformin and vandetanib for at least 4 weeks to establish steady-state. Comparisons of metformin exposure between cycle 2 (with vandetanib) and first-dose (alone) will determine the extent of drug-interaction (if any) with vandetanib.

Bioanalytical measurements of metformin and vandetanib will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Blood Processing Core Lab.

The PK sampling will also be used to monitor vandetanib and metformin exposure metrics in order to correlate to pharmacodynamic endpoints, clinical response, toxicity, and pharmacogenetic analyses.

5.2.2 Pharmacogenetic Studies

One blood sample per patient will be collected in a purple top tube for pharmacogenetic studies to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET). DNA will be analyzed on a DMET Plus (Affymetrix) genotyping platform that tests for 1,936 genetic variations in 225 drug disposition genes, including 47 CYP (phase I metabolism) genes, 13 non-CYP (phase I metabolism) genes, 78 phase II metabolizing genes (including UGTs), 63 transporters, 4 genes involved in facilitation of drug transporters, 9 genes involved in global regulation of drug metabolizing/transporting proteins, 4 drug binding proteins, and 4 drug targets.

Of particular interest to vandetanib pharmacological actions (and hypothesized interaction with metformin) is the inhibition of MATE1, MATE2K, and OCT2. The presence of SNPs in the genes encoding these transporters may alter the PK of the drug combination and any interaction. MATE1 and MATE2K are not included in the DMET platform (OCT2 is), therefore genetic analysis for MATE1 and MATE2K will be performed using direct sequencing, Taqman genotyping, or multiplexed genotyping as needed.

5.2.3 Handling and Processing of Specimens

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

Upon arrival in the Blood Processing Core, samples will be centrifuged and the plasma transferred into cryovials for storage at -80 C until the time of analysis. In addition, samples will be barcoded as described in Section **5.2.4**.

5.2.4 Blood Processing Core (BPC)– Storage

All samples will be bar-coded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients with LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer locations. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (e.g. delay in sample processing, storage conditions on the ward, etc).

Bar-coded samples are stored in bar-coded boxes in locked freezers at either -20 C or -80 C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age,

dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

All radiographic images will be stored in the Dept. of Radiology, Clinical Center, NIH and will be reviewed by NIH CC staff radiologists.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) 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.

All Adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 60 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

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.

6.1.1 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 subject 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

6.2 RESPONSE CRITERIA

For the purposes of this study, patients should initially be re-evaluated for response every 8 weeks during the first 32 weeks and every 12 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response. (See section **3.4.3** for restaging assessments.)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.2.1 Definitions

- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with vandetanib or metformin.
- Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)
- Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.2.2 Disease Parameters

6.2.2.1 Measurable disease

- Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:
    - By chest x-ray: ≥ 20 mm
    - By CT scan:
        - Scan slice thickness 5 mm or under: ≥10 mm
        - Scan slice thickness 5 mm or under: double the slice thickness
    - With calipers on clinical exam: ≥ 10 mm

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

6.2.2.2 Non-measurable disease

- All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

6.2.2.3 Target Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

6.2.2.4 Non-target lesions

- All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.2.3 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. 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). 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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  MRI is also acceptable in certain situations (e.g. for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (26) or surgical resection is an endpoint.

- Cytology, Histology: These techniques can be used to differentiate between partial responses (14) and complete responses (26) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.2.4.2 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

- Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

6.2.4.3 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.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

6.2.5 Confirmatory Measurement/Duration of Response

6.2.5.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 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.

6.2.5.2 Duration of Response

- 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 progressive disease is objectively documented.

- 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, including the baseline measurements.
- Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. http://www.ncbi.nlm.nih.gov/pubmed/18711427?dopt=Abstract

6.3 TOXICITY CRITERIA

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).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 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.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)

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

7.1.9 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.

7.1.10 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.

7.2 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

7.3 NCI IRB AND CLINICAL DIRECTOR (CD) REPORTING

7.3.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

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

- 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. Deviations from the protocol that are beyond the control of the investigators/research team or those that occur to accommodate reasonable patient needs or to ensure patient safety will not be reported.

7.3.2 NCI-IRB Requirements for PI Reporting of Adverse Events 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.

7.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

The Institution must report the following information to the Sanofi Genzyme Pharmacovigilance

1. Routine transmission of SAEs related to the use of the Sanofi Genzyme product must be transmitted **within 1 business day** of the Institution's awareness or identification of the event via a MedWatch form. When reporting, a cover page should accompany the MedWatch form indicating the following:

    - Investigator Sponsored Study (ISS)

- The investigator's name and address
- The trial name/title and Sanofi Genzyme ISS reference number
- Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

2. New Safety Findings in a study pertaining to safety of product must be transmitted within 1 business day.

Sanofi Genzyme Pharmacovigilance Contact

CL-CPV-Receipt@sanofi.com

Fax: + 33 1 60 49 70 70

Institution will also inform Sanofi Genzyme on any complaints on the Product to Clinical Pharmacy Research Services (CPRS) at CPRSProductComplaints@genzyme.com), immediately, but in any event within one (1) business day, after becoming aware of the complaint.

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

A committee made up of the Principal Investigator, Ramaprasad Srinivasan, M.D., Ph.D. (or designee), a Research Nurse associated with the trial and other UOB clinical staff will review the events of all patients on the protocol periodically (typically at least once every two weeks). Follow-up of both on-going and previously treated patients and the reported adverse events in a given week will be reviewed (that is, adverse events, protocol adherence, tumor responses, and potential new patient eligibility etc.). Any safety concerns or new information that might affect either the ethical and/or scientific conduct of the trial, or protocol deviations will be reported to the NCI IRB and Sanofi Genzyme in written form. If trends are noted and/or risks warrant it, accrual will be interrupted and/or the protocol and/or the consent will be modified accordingly.

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 STATISTICAL CONSIDERATIONS

8.1 PHASE I COMPONENT

The objective of the phase 1 portion of the study is to establish the safety and maximum tolerated dose (MTD) of vandetanib and metformin when used in combination in patients with metastatic RCC. The study design is based on a single arm, fixed order dose-escalation Phase 1 study using a modified Fibonacci schema.

Dose escalation will proceed in cohorts of 3-6 patients each as outlined below. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during 1 cycle of treatment

(42 days from the time the intended dose of metformin is reached for a given dose level), and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of the experimental regimen.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter up to 3 patients at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level	This is the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

8.2 PHASE II COMPONENT

The goal of the phase II component of this study is to establish whether treatment with vandetanib and metformin in patients with metastatic HLRCC/SDH associated RCC and papillary renal cancer results in an adequate overall response rate to warrant further development.

Patients will be enrolled in two cohorts:

- Cohort I: Patients with metastatic HLRCC/SDH associated renal cancer
- Cohort II: Patients with sporadic/non-HLRCC papillary renal cancer.

The study will be designed with a Simon two-stage optimal design which will be stratified by the two cohorts (i.e., separate design for each cohort). In each cohort, 7 patients will be accrued in the first stage. If there are no responses (either CR or PR) in 7 patients, accrual to the cohort will be terminated, and the treatment will be considered ineffective for the cohort. If at least one patient responds among the 7 patients then 14 additional patients will be accrued to the cohort. If 3 or more patients of 21 respond then the treatment will be considered worthy of future investigation

for that cohort. In either cohort, if fewer than 3 patients respond, the treatment will not be considered worthy of additional investigation for that cohort.

For each cohort, the two-stage optimal design is based on assuming an ineffective response rate of 5% and a targeted effective response rate of 30%. We also assume that the probability of accepting an ineffective treatment and the probability of rejecting an effective treatment are each 10%. With this design, we have a 70% chance of stopping accrual to a cohort at the end of the first stage if the response rate in that cohort is 5%.

Secondary objectives are listed in Section **1.1.2.** The follow-up times for biomarker endpoints are given in Section **5.1**. Analyses will focus on comparing changes in these biomarkers on treatment from the pre-study measurement. Longitudinal changes in continuous biomarkers 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 incorporate all follow-up times when evaluating change). Evaluation of time to progression and progression-free survival will be based on restaging studies performed as outlined and will be summarized using Kaplan-Meier curves.

8.3 ACCRUAL CEILING

In the phase I portion of the study, up to 6 patients may be enrolled in a specific dose combination cohort. Based on the assumption that 4 dose levels will be evaluated, the total number of evaluable patients will be 24. To allow for a few patients who may be inevaluable, the accrual ceiling for this portion of the study will be set at 27. Based on how dose escalation proceeds and the adverse events seen, the total number of patients to be accrued may be changed via a protocol amendment.

The accrual ceiling for the phase II component of the study is 21 evaluable patients for each cohort. To allow for inevaluable patients, the accrual ceiling will be set at 23 patients in each phase II cohort.

The overall accrual ceiling for the study including both the phase I and phase II components will therefore be set at 73. With an expected accrual in the phase I component of 12-15 patients per year, we expect to complete accrual for this portion of the study within 1–2 years. With an expected accrual of 8-12 patients per year for each phase II cohort, we expect to complete accrual within 2-3 years. Therefore, overall study is expected to have completed accrual within 4-5 years.

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

The agent (vandetanib) supplied by Sanofi Genzyme used in this protocol is provided to the NCI CCR under a Cooperative Research and Development Agreement (CRADA) between Sanofi Genzyme [hereinafter referred to as Collaborator], CRADA# 02050 and 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 Agents in this study:

Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agents are confidential and proprietary to Collaborator 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.

For a clinical protocol where there is an investigational Agent used in combination with other investigational Agents, 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".)

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.

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

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.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale For Subject Selection

10.1.1 Research subject selection

Subjects of both genders and from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria. Pregnant women are excluded from participation in the trial because vandetanib can cause fetal harm when administered to a pregnant woman. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

10.1.2 Participation of children

This protocol will exclude children below 18 years of age since there are no safety data available in this group of patients.

10.2 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.3.1**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures

described in MAS Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.3 Evaluation of Benefits and Risks/Discomforts

10.3.1 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.

10.3.2 Potential risks

Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section, the product package inserts and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as previously described. Experience with the agents to date suggests that these agents are associated with an acceptable toxicity profile.

We will encourage all subjects to complete a research advance directive at enrollment.

10.3.2.1 Optional Biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.3.2.2 Research Radiation Risks

Biopsies may be performed with CT guidance and a PET scan for research may be performed. If that is the case, then this research study involves exposure to radiation from 1 FDG PET/CT scan on cycle 1 day 15 and up to 2 CT scans for CT guided biopsy, with combined effective dose of 2.4 rem. This is below the guideline of 5.0 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

10.4 Alternative Treatments

Patients will be apprised of other therapeutic options, both experimental and those of standard of care.

10.5 Consent Processes and Documentation

An associate 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 his/her questions will be answered. After a decision is made to enroll into the study, the patient will be asked to sign the consent document to indicate willing informed consent to participate in the trial. For the optional biopsy for research in the protocol, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

10.5.1 Telephone -Consent

In the case that reconsent is needed, we are requesting that the telephone consent process be used. In this case, the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator.

10.5.2 Informed Consent of Non-English Speaking Subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).
We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 VANDETANIB

(Please see vandetanib package insert for complete information)

11.1.1 Source

Vandetanib is commercially available under the trade name CAPRELSA®, but will be supplied by the manufacturer (Sanofi Genzyme) for the purposes of the study.

11.1.2 Toxicity

The following adverse events have been reported in patients treated with vandetanib: Rash, diarrhea, nausea and vomiting, ECG abnormalities (ST and T wave changes, QTc prolongation), hypertension, increased serum LDH, lymphopenia, elevation of AST/ALT/ alkaline phosphatase, anorexia, nausea, headache, elevation of serum creatinine, hypertriglyceridemia, leukopenia,

tinnitus, thrombocytopenia, fatigue, abdominal pain, back pain, fever , cough, peripheral edema , insomnia, hematuria, dyspnea, proteinuria.

The most serious adverse event associated with metformin administration is lactic acidosis, which is overall a rare event (0.03 cases/1000 patient – years, with approximately 0.015 fatal cases/1000 patient – years). The risk of lactic acidosis associated with metformin is increased in patients with renal insufficiency, congestive heart failure, hepatic disease, recent surgery, or any condition associated with hypoxemia, severe dehydration, or sepsis. More common side effects that are associated with metformin administration include: Diarrhea, nausea and vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Less common side effects include: abnormal stools, hypoglycemia, myalgia, lightheadedness, dyspnea, nail disorder, rash, diaphoresis, changes in taste, chest discomfort, palpitations, chills, flu syndrome, and flushing.

11.1.3 Formulation and preparation

Vandetanib is available in 100mg and 300mg tablets.

11.1.4 Stability and Storage

Vandetanib should be stored at approximately 25ºC, with excursion permitted to 15º- 30ºC.

11.1.5 Administration procedures

Vandetanib is a tablet that is taken orally.

11.1.6 Incompatibilities

Co-administration of vandetanib and drugs with potent CYP3A4 inducer effects are not allowed. Agents with potent inhibitory effects on CYP3A4 should be avoided where possible. Other agents with some modulation of and/or metabolization through CYP3A4 can be used with caution at the discretion of the Principal Investigator. Vandetanib should also not be administered in patients receiving drugs known to prolong QT interval or induce torsades de pointes. No concurrent systemic anti-neoplastic therapy for RCC will be allowed.

11.2 METFORMIN

(Please see metformin package insert for complete information)

11.2.1 Source

Metformin is commercially available and manufactured by Bristol-Myers Squibb Company (Princeton, NJ) under the trade name GLUCOPHAGE®.

11.2.2 Toxicity

The most serious adverse event associated with metformin administration is lactic acidosis, which is overall a rare event (0.03 cases/1000 patient – years, with approximately 0.015 fatal cases/1000 patient – years). The risk of lactic acidosis associated with metformin is increased in patients with renal insufficiency, congestive heart failure, hepatic disease, recent surgery, or any condition associated with hypoxemia, severe dehydration, or sepsis. More common side effects that are associated with metformin administration include: Diarrhea, nausea and vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Less common side effects include:

abnormal stools, hypoglycemia, myalgia, lightheadedness, dyspnea, nail disorder, rash, diaphoresis, changes in taste, chest discomfort, palpitations, chills, flu syndrome, and flushing.

11.2.3 Formulation and preparation

Metformin is available in 500mg, 850mg, and 1000mg tablets. Immediate-release formulation will be used. If necessary to achieve desired dose, tablets will be split.

11.2.4 Stability and Storage

Metformin should be stored at approximately 20º-25ºC, with excursion permitted to 15º-30ºC.

11.2.5 Administration procedures

Metformin is a tablet that is taken orally.

11.2.6 Incompatibilities

Metformin is contraindicated in patients with 1. renal disease or renal dysfunction which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; 2. Known hypersensitivity to metformin hydrochloride; 3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. The NIH/CCC protocol for withholding of metformin during such procedures will be used.

Concomitant administration of furosemide, nifedipine, and other cationic drugs can lead to increased plasma levels of metformin. Close monitoring of subjects who take such medications will be undertaken to evaluate for potential toxicity.

12 REFERENCES

(1) Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30.
(2) Linehan WM, Pinto PA, Bratslavsky G, Pfaffenroth E, Merino M, Vocke CD, et al. Hereditary kidney cancer: unique opportunity for disease-based therapy. Cancer 2009;115:2252-61.
(3) Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 2002;30:406-10.
(4) Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003;73:95-106.
(5) Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Am J Surg Pathol 2007;31:1578-85.
(6) Mullen AR, Wheaton WW, Jin ES, Chen PH, Sullivan LB, Cheng T, et al. Reductive carboxylation supports growth in tumour cells with defective mitochondria. Nature 2012;481:385-8.
(7) Ooi A, Wong JC, Petillo D, Roossien D, Perrier-Trudova V, Whitten D, et al. An antioxidant response phenotype shared between hereditary and sporadic type 2 papillary renal cell carcinoma. Cancer Cell 2011;20:511-23.
(8) Pollard PJ, Briere JJ, Alam NA, Barwell J, Barclay E, Wortham NC, et al. Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. Hum Mol Genet 2005;14:2231-9.
(9) Isaacs JS, Jung YJ, Mole DR, Lee S, Torres-Cabala C, Chung YL, et al. HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: novel role of fumarate in regulation of HIF stability. Cancer Cell 2005;8:143-53.
(10) Tong WH, Sourbier C, Kovtunovych G, Jeong SY, Vira M, Ghosh M, et al. The glycolytic shift in fumarate-hydratase-deficient kidney cancer lowers AMPK levels, increases anabolic propensities and lowers cellular iron levels. Cancer Cell 2011;20:315-27.
(11) Ricketts CJ, Shuch B, Vocke CD, Metwalli AR, Bratslavsky G, Middelton L, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol 2012;188:2063-71.
(12) Ricketts CJ, Forman JR, Rattenberry E, Bradshaw N, Lalloo F, Izatt L, et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat 2010;31:41-51.
(13) Ciardiello F, Caputo R, Damiano V, Caputo R, Troiani T, Vitagliano D, 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 2003;9:1546-56.
(14) Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 2002;62:4645-55.

(15) ZD6474 Investigator's Brochure. 2013. Wilmington, DE, US Drug Development, Astra-Zeneca Pharmaceuticals.

Ref Type: Generic

(16) Hennequin LF, Stokes ES, Thomas AP, Johnstone C, Ple PA, Ogilvie DJ, et al. Novel 4-anilinoquinazolines with C-7 basic side chains: design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors. J Med Chem 2002;45:1300-12.

(17) Holden SN, Eckhardt SG, Basser R, de BR, Rischin D, Green M, et al. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. Ann Oncol 2005;16:1391-7.

(18) Tamura T, Minami H, Yamada Y, Yamamoto N, Shimoyama T, Murakami H, et al. A phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. J Thorac Oncol 2006;1:1002-9.

(19) Natale RB, Bodkin D, Govindan R, Sleckman BG, Rizvi NA, Capo A, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase ii study. J Clin Oncol 2009;27:2523-9.

(20) Heymach JV, Johnson BE, Prager D, Csada E, Roubec J, Pesek M, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. J Clin Oncol 2007;25:4270-7.

(21) Kiura K, Nakagawa K, Shinkai T, Eguchi K, Ohe Y, Yamamoto N, et al. A randomized, double-blind, phase IIa dose-finding study of Vandetanib (ZD6474) in Japanese patients with non-small cell lung cancer. J Thorac Oncol 2008;3:386-93.

(22) Wells SA, Jr., Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010;28:767-72.

(23) Robinson BG, Paz-Ares L, Krebs A, Vasselli J, Haddad R. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010;95:2664-71.

(24) Boer K, Lang I, Llombart-Cussac A, Andreasson I, Vivanco GL, Sanders N, et al. Vandetanib with docetaxel as second-line treatment for advanced breast cancer: a double-blind, placebo-controlled, randomized Phase II study. Invest New Drugs 2012;30:681-7.

(25) Miller KD, Trigo JM, Wheeler C, Barge A, Rowbottom J, Sledge G, et al. A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. Clin Cancer Res 2005;11:3369-76.

(26) Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134-41.

(27) Lee JS, Hirsh V, Park K, Qin S, Blajman CR, Perng RP, et al. Vandetanib Versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). J Clin Oncol 2012;30:1114-21.

(28) Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011;29:1059-66.

(29) Herbst RS, Sun Y, Eberhardt WE, Germonpre P, Saijo N, Zhou C, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol 2010;11:619-26.

(30) de Boer RH, Arrieta O, Yang CH, Gottfried M, Chan V, Raats J, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. J Clin Oncol 2011;29:1067-74.

(31) Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol 2012;13:897-905.

(32) Xiao YY, Zhan P, Yuan DM, Liu HB, Lv TF, Shi Y, et al. Chemotherapy plus Vandetanib or chemotherapy alone in advanced non-small cell lung cancer: a meta-analysis of four randomised controlled trials. Clin Oncol (R Coll Radiol) 2013;25:e7-e15.

(33) Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010;33:1304-8.

(34) Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304-5.

(35) El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 2000;275:223-8.

(36) Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167-74.

(37) Marsin AS, Bertrand L, Rider MH, Deprez J, Beauloye C, Vincent MF, et al. Phosphorylation and activation of heart PFK-2 by AMPK has a role in the stimulation of glycolysis during ischaemia. Curr Biol 2000;10:1247-55.

(38) Winder WW, Wilson HA, Hardie DG, Rasmussen BB, Hutber CA, Call GB, et al. Phosphorylation of rat muscle acetyl-CoA carboxylase by AMP-activated protein kinase and protein kinase A. J Appl Physiol 1997;82:219-25.

(39) Choueiri TK, Vaishampayan U, Rosenberg JE, Logan TF, Harzstark AL, Bukowski RM, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. J Clin Oncol 2013;31:181-6.

(40) Ooi A, Dykema K, Ansari A, Petillo D, Snider J, Kahnoski R, et al. CUL3 and NRF2 mutations confer an NRF2 activation phenotype in a sporadic form of papillary renal cell carcinoma. Cancer Res 2013;73:2044-51.

13 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

14 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.

Class	**Symptoms**
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.

15 APPENDIX C: MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES (TDP)

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 Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

15.1 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. In subjects who have discontinued use of these drugs, at least five half-lives of the drug must have elapsed before the first scheduled dose of vandetanib (at least four weeks for levomethadyl). These drugs should also be avoided for **up to 4 weeks following discontinuation of study treatment:**

Table 2 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Amiodarone	Anti-arrhythmic/abnormal heart rhythm	Females>Males,TdP risk regarded as low
Anagrelide	Thromobocytopenia	
Arsenic trioxide	Anti-cancer/Leukemia	
Astemizole	Antihistamine/Allergic rhinitis	No Longer available in U.S.
Azithromycin	Antibiotic/bacterial infection	
Bepridil	Anti-anginal/heart pain	Not available in U.S.
Chloroquine	Anti-malarial/malaria infection	
Chlorpromazine	Anti-psychotic/Anti-emetic/schizophrenia/ nausea	
Cisapride	GI stimulant/heartburn	No longer available in U.S.
Citalopram	Anti-depressant/depression	
Clarithromycin	Antibiotic/bacterial infection	
Cocaine	Topical anesthetic	
Disopyramide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Dofetilide	Anti-arrhythmic/abnormal heart rhythm	Females > Males
Domperidone	Anti-nausea/nausea	Not available in U.S.
Dronedarone	Atrial fibrillation	
Droperidol	Sedative;Anti-nausea/anesthesia adjunct, nausea	
Erythromycin	Antibiotic;GI stimulant/bacterial infection; increase GI motility	Females>Males
Escitalopram	Major depression/anxiety disorders	

Table 2 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Flecainide	Anti-arrhythmic/abnormal heart rhythm	
Halofantrine	Anti-malarial/malaria infection	Females>Males
Haloperidol	Anti-psychotic/schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Levofloxacin	Bacterial infection	
Levomethadyl	Opiate agonist/pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Anti-psychotic/schizophrenia	Not available in U.S.
Methadone	Opiate agonist/pain control, narcotic dependence	Females>Males
Moxifloxacin	Antibiotic/bacterial infection	
Ondansetron	Nausea, vomiting	
Pentamidine	Anti-infective/pneumocystis pneumonia	Females>Males
Pimozide	Anti-psychotic/Tourette's tics	Females>Males
Probucol	Antilipemic/Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic/abnormal heart rhythm	
Quinidine	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sevoflurane	General anesthetic	
Sotalol	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sparfloxacin	Antibiotic/bacterial infection	No longer available in U.S.
Sulpride	Anti-psychotic/schizophrenia	Not available in U.S.
Terfenadine	Antihistamine/Allergic rhinitis	No longer available in U.S.
Thioridazine	Anti-psychotic/schizophrenia	
Vandetanib (*Does not apply to this study)	Anti-cancer/Thyroid cancer	

[a] Source: www.QTdrugs.org. Last revised: 26 September 2014

15.2 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 should be avoided when possible during the study. In subjects who have discontinued use of these drugs, at least five half-lives of the drug must have elapsed before the first scheduled dose of vandetanib. 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 (reference Section **3.3** of the protocol).

Table 3 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Alfuzosin	Alpha1-blocker/Benign prostatic hyperplasia	
Apomorphine	Dopaminergic/Anti-viral/Anti-infective/ Parkinson's Disease	
Aripiprazole	Anti-psychotic/ Psychosis/Depression	
Atazanavir	Protease inhibitor/HIV	
Bortezomib	Proteasome inhibitor/Multiple myeloma/ lymphoma	
Bosutinib	Tyrosine kinase inhibitor/ Leukemia	
Clozapine	Anti-psychotic/schizophrenia	
Crizotinib	Kinase inhibitor/ anti-cancer	
Dabrafenib	Anti-cancer/ melanoma	
Dasatinib	Tyrosine kinase inhibitor/ leukemia	
Dexmedetomine	Anti-malarial	
Dihydroartemisinin+ piperaquine	Anti-malarial	
Dolasetron	Anti-nausea/nausea, vomiting	
Dronedarone	Anti-arrhythmic/Atrial Fibrillation	
Eribulin	Anti-cancer/metastatic breast neoplasias	
Famotidine	H2-receptor antagonist/Peptic ulcer/ GERD	
Felbamate	Anti-convulsant/seizure	
Fingolimod	Immunosuppressant/Multiple Sclerosis	
Foscarnet	Anti-viral/HIV infection	
Fosphenytoin	Anti-convulsant/seizure	
Gatifloxacin	Antibiotic/bacterial infection	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Antibiotic/bacterial infection	
Granisetron	Anti-nausea/nausea and vomiting	

Table 3 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Iloperidone	Antipsychotic, atypical/Schizophrenia	
Isradipine	Anti-hypertensive/high blood pressure	
Lapatinib	Anti-cancer/breast cancer, metastatic	
Lithium	Anti-mania/bipolar disorder	
Mifepristone	Progesterone antagonist/ Pregnancy termination	
Mirabegron	Beta3 adrenergic antagonist/ Overactive bladder	
Mirtazapine	Anti-depressant, Tetracyclic/ Depression	
Moexipril/HCTZ	Anti-hypertensive/high blood pressure	
Nicardipine	Anti-hypertensive/high blood pressure	
Nilotinib	Anti-cancer/Leukemia	
Norfloxacin	Antibiotic	
Ofloxacin	Antibiotic/bacterial infection	
Olanzapine	Anti-psychotic, atypical/ Schizophrenia, bipolar	
Oxytocin	Oxytocic/Labor stimulation	
Paliperidone	Antipsychotic, atypical/Schizophrenia	
Pasireotide	Somatostatin analog/ Cushings Disease	
Pazopanib	Tyrosine kinase inhibitor/ Anti-cancer	
Perflutren lipid microspheres	Imaging contrast agent/Echocardiography	
Pipamperone	Anti-psychotic/schizophrenia	Not available in U.S.
Promethazine	Anti-psychotic / Anti-emetic. nausea	
Quetiapine	Anti-psychotic/schizophrenia	
Ranolazine	Anti-anginal/chronic angina	
Rilpivirine	Anti-viral/ HIV/AIDS	
Risperidone	Anti-psychotic/schizophrenia	
Roxithromycin*	Antibiotic/bacterial infection	*Not available in U.S.
Saquinavir	Anti-viral/ HIV/AIDS	
Sertindole	Antipsychotic, atypical/Anxiety, Schizophrenia	Not available in U.S.
Sorafenib	Tyrosine kinase inhibitor/ Anti-cancer	
Sunitinib	Anti-cancer/RCC, GIST	
Tacrolimus	Immunosuppressant/Immune suppression	
Tamoxifen	Anti-cancer/breast cancer	
Telavancin	Antibiotic	

Table 3 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Telithromycin	Antibiotic/bacterial infection	
Tetrabenazine	Monoamine Transporter Inhibitor/ Chorea (Huntington's disease)	Orphan drug in US
Tizanidine	Muscle relaxant/	
Tolterodine	Muscle relaxant/ Bladder spasm	
Toremifene	Estrogen agonist/antagonist/ Anti-cancer	
Vardenafil	phosphodiesterase inhibitor/vasodilator	
Vemurafenib	Kinase inhibitor/ Anti-cancer	
Venlafaxine	Anti-depressant/depression	
Vorinostat	Anti-cancer/ lymphoma	
Ziprasidone	Anti-psychotic/schizophrenia	

[a] Source: www.QTdrugs.org. Last revised: 26 September 2014

16 APPENDIX D: PATIENT DRUG AND SIDE EFFECTS DIARY

16.1 LEAD IN CYCLE

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each Cycle.
2. You will take ___ vandetanib(V) pill each day.
3. You will take ___ metformin (M) pills twice each day.
4. Record the date and time you took each dose of study medication. Take the medication together in the AM.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring your pill bottles and this form to your physician when you go for your next appointment.

Date	Day	Time of Dose 1	Drug(s) taken	Comments/ Symptoms	Time of Dose 2	Drug(s) taken	Comments/ Symptoms
	-14		M V			M	
	-13		M V			M	
	-12		M V			M	
	-11		M V			M	
	-10		M V			M	
	-9		M V			M	
	-8		M V			M	
	-7		M V			M	
	-6		M V			M	
	-5		M V			M	
	-4		M V			M	
	-3		M V			M	
	-2		M V			M	
	-1		M V			M	

Signature: _____ Date_____

16.2 ALL OTHER CYCLES

Level 1

Cycle #_____

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Complete for each Cycle.
2. You will take ___ vandetanib(V) pill _____ each day.
3. You will take ___ metformin (M) pill each day.
4. Record the date and time you took each dose of study medication; take the medications together in the AM.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring your pill bottles and this form to your physician when you go for your next appointment.

Date	Day	Time of Dose	Drug(s) taken	Comments/ Symptoms
	1		M V	
	2		M V	
	3		M V	
	4		M V	
	5		M V	
	6		M V	
	7		M V	
	8		M V	
	9		M V	
	10		M V	
	11		M V	
	12		M V	
	13		M V	

Date	Day	Time of Dose	Drug(s) taken	Comments/ Symptoms
	14		M V	
	15		M V	
	16		M V	
	17		M V	
	18		M V	
	19		M V	
	20		M V	
	21		M V	
	22		M V	
	23		M V	
	24		M V	
	25		M V	
	26		M V	
	27		M V	
	28		M V	

Signature: _____ Date: _____

Level 2, Level 3, Level 4

Cycle #_____

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Complete for each Cycle.
2. You will take ___ vandetanib(V) pill each day.
3. You will take ___ metformin (M) pills each day.
4. Record the date and time you took each dose of study medication; take the medications together in the AM.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring your pill bottles and this form to your physician when you go for your next appointment.

Date	Day	Time of Dose 1	Drug(s) taken	Comments/ Symptoms	Drug(s) taken	Time of Dose 2	Comments/ Symptoms
	1		M V		M		
	2		M V		M		
	3		M V		M		
	4		M V		M		
	5		M V		M		
	6		M V		M		
	7		M V		M		
	8		M V		M		
	9		M V		M		
	10		M V		M		
	11		M V		M		
	12		M V		M		
	13		M V		M		

Date	Day	Time of Dose 1	Drug(s) taken	Comments/ Symptoms	Drug(s) taken	Time of Dose 2	Comments/ Symptoms
	14		M V		M		
	15		M V		M		
	16		M V		M		
	17		M V		M		
	18		M V		M		
	19		M V		M		
	20		M V		M		
	21		M V		M		
	22		M V		M		
	23		M V		M		
	24		M V		M		
	25		M V		M		
	26		M V		M		
	27		M V		M		
	28		M V		M		

Signature: _____ Date: _____

17 APPENDIX E: PATIENT INSTRUCTIONS FOR METFORMIN / VANDETANIB

You are a participant in a Clinical Trial of 2 medications: Metformin and Vandetanib. The following are important reminders while you are taking the medications.

You will be responsible for maintaining 2 diaries while on the clinical trial; please bring your diaries with you to each visit:

1. Blood Pressure Diary
2. Pill and Side Effect Diary

With the exception of the first day you are on the trial, you will be taking both medications every day. Take the medications together with a full glass of water after eating a light breakfast. Record the date and time you take the medications on your diary. If you are taking the Metformin in the AM and PM, take the evening dose of Metformin 12 hours after your AM dose. Do not start any **NEW** medications before checking with the study team.

Record your Blood Pressure daily on your BP diary. Sit quietly for 5 min before you check your BP. If your reading on the top is above 140, or the reading on the bottom is above 90, sit quietly for 10 min and recheck your BP. If it remains elevated, contact the team immediately at one of the numbers below.

Please wear sunscreen (at least SPF 30) when outside, and minimize your sun exposure.

Please have a thermometer in order to check your temperature if directed to do so.

If you should need dental work or surgery, notify your team immediately.

Do not drink alcohol (including beer and wine) unless approved by the doctor or nurse.

If you are of reproductive age, you **MUST** practice birth control.

When scheduled for a CAT Scan, do not take your Metformin the morning of the scan. Do not resume the metformin until you have had your labs to check your kidney function, and are told to resume the Metformin by the doctor or nurse.

You will be given medication at the beginning of the trial to be used only as needed. If you need any of these medications, follow the directions on the label, and record that you have taken the medication in your diary. These medications are: 1.Chlorpromazine (Nausea); 2.Loperimide (Diarrhea); 3.Colace (Constipation)

You will be obtaining bloodwork and an EKG at home once a week as directed by the Study Team. The EKG must be done at least **4-8 hours after your AM dose of Vandetanib**, so be sure to schedule your appointments with your PCP at the correct time.

Please call your study team with ANY questions or change in your condition.

Martha Ninos RN (Study Coordinator)	**240-760-6248 (Mon-Fri: 8-4PM) *****
Julia Friend PA-C	**301-240-4759 (Mon-Fri: 8-4PM) *****

***** Evenings, weekends, and emergencies call Hospital paging @ 301-496-1211 and ask to speak to the Urology Fellow On Call**

18 APPENDIX F: BLOOD PRESSURE MONITORING FORM

18.1 LEAD IN CYCLE

Instructions

1. Take your blood pressure at least once per day during each cycle of study drug
2. Record the date you took your blood pressure and your blood pressure below
3. Bring this form with you at your next study visit

Cycle Day	Date	Blood Pressure
-14	_____	_____/_____
-13	_____	_____/_____
-12	_____	_____/_____
-11	_____	_____/_____
-10	_____	_____/_____
-9	_____	_____/_____
-8	_____	_____/_____
-7	_____	_____/_____
-6	_____	_____/_____
-5	_____	_____/_____
-4	_____	_____/_____
-3	_____	_____/_____
-2	_____	_____/_____
-1	_____	_____/_____

Signature: _____ Date_____

18.2 ALL OTHER CYCLES

Instructions

1. Take your blood pressure at least once per day during each cycle of study drug
2. Record the date you took your blood pressure and your blood pressure below
3. Bring this form with you at your next study visit

Cycle Day	Date	Blood Pressure
1	_____	_____/_____
2	_____	_____/_____
3	_____	_____/_____
4	_____	_____/_____
5	_____	_____/_____
6	_____	_____/_____
7	_____	_____/_____
8	_____	_____/_____
9	_____	_____/_____
10	_____	_____/_____
11	_____	_____/_____
12	_____	_____/_____
13	_____	_____/_____
14	_____	_____/_____
15	_____	_____/_____

Cycle Day	Date	Blood Pressure
16	_____	_____/_____
17	_____	_____/_____
18	_____	_____/_____
19	_____	_____/_____
20	_____	_____/_____
21	_____	_____/_____
22	_____	_____/_____
23	_____	_____/_____
24	_____	_____/_____
25	_____	_____/_____
26	_____	_____/_____
27	_____	_____/_____
28	_____	_____/_____

Signature: _____ Date: _____