MC1152

Mayo Clinic Cancer Center

A Phase II Efficacy Trial of Pazopanib in Non-Clear Cell Metastatic Renal Cell Cancer (mRCC) PINCR

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Drug Availability

Drug Company Supplied: Pazopanib, GW786034 – NSC 737754

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
Patient eligibility, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist Phone: [redacted] E-mail: [redacted]
Forms completion and submission	[redacted] Phone: [redacted] Email: [redacted]
Protocol document, consent form, regulatory issues	[redacted], Research Protocol Specialist Phone: [redacted] Email: [redacted]
Non-paraffin biospecimens	[redacted] Phone: [redacted] Email: [redacted]
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	[redacted] Phone [redacted] E-mail: [redacted]

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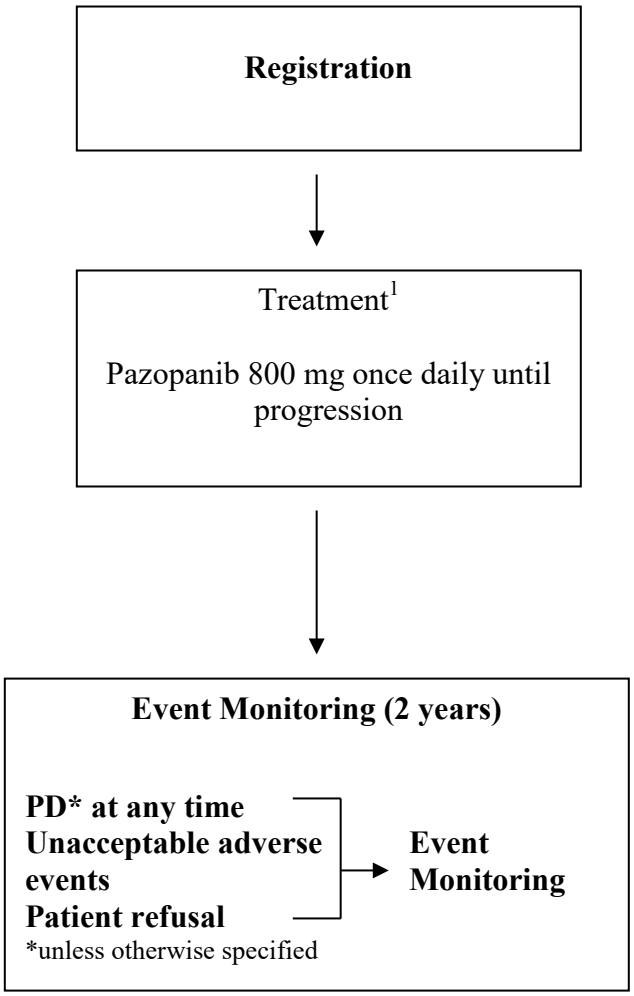
Study Schema



If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

[1] Cycle length=28 days

Generic name: Pazopanib Mayo abbreviation: 786034 Availability: Novartis

1.0 Introduction

1.1 Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a non-homogenous collection of histologically distinct tumor types broadly classified as clear cell and non-clear cell kidney cancer as recognized by the Heidelberg classification system. While clear cell histology forms the bulk (75-80%) (Cohen and McGovern 2005) of all kidney cancers several distinct non clear cell histological subtypes constitute 15-25% of all renal cell cancers. The approximate distribution among histological sub-types of kidney cancer is as follows:

Clear cell (75 to 85 percent of tumors)

Chromophilic (papillary) (10 to 15 percent)

Chromophobic (5 to 10 percent)

Oncocytic (uncommon)

Collecting duct (Bellini's duct) (very rare)

The genetic and molecular biology of clear cell renal cancer has been successfully targeted with the approval of several new drugs that inhibit the vascular endothelial growth factor (VEGF) and the mammalian-target of rapamycin (m-TOR) pathways since 2006 (Di Lorenzo, Autorino et al. 2009). These pathways are up regulated as a result of mutational inactivations in the Von Hippel-Lindau (VHL) gene that inhibition of these pathways using pazopanib (LaPlant and Louzon), sunitinib (Motzer, Hutson et al. 2007), sorafenib (Escudier, Eisen et al. 2007), everolimus (Motzer, Escudier et al. 2008), bevacizumab with interferon (Rini, Halabi et al. 2008) and temsirolimus (Hudes, Carducci et al. 2007) has resulted in slowing disease progression and prolonging longevity of life in the metastatic setting compared to previous cytokine based approaches for progressive stage IV disease.

Most of the above trials however excluded non clear cell histological subtypes, and it remains unclear if patients with metastatic non clear cell histology will derive therapeutic benefit from the above drugs as well, since the genetic and molecular characteristics of non clear cell histology are distinct and the clinical behavior of these histological subtypes are different from clear cell histology. For example, when initially diagnosed in the localized stage, papillary, chromophobe and oncocytomas have a better prognosis than clear cell renal cancer. However, after developing metastases, in general the survival of patients with non clear cell RCC becomes universally poor. The exception is collecting duct cancers (including medullary) of the kidney, which are extremely aggressive and carry a poor prognosis in any stage of detection.

At the molecular and genetic level the characteristics of non clear cell vary with histology. Papillary RCC, the second most common histological subtype is histologically categorized into Type I and Type II. Type I (sporadic and hereditary forms) is associated with activating mutations of the methyl-nitroso-nitroguanidine-induced (MET) oncogene on the long arm of chromosome 7 (Dharmawardana, Giubellino et al. 2004). These mutations result in ligand independent activation of intracytoplasmic tyrosine kinase domains, which constitutively activate hepatocyte growth factor (HGF)/MET pathway. Additionally in its

hereditary form families with Type I papillary RCCC have germline mutations in MET oncogene which are passed on to offspring with variable penetrance. Individuals with these mutant alleles phenotypically present with bilateral multifocal papillary Type I RCCs (Sudarshan and Linehan 2006). Papillary Type II RCC on the other hand can present in its hereditary form with leiomyomatosis (Hereditary leiomyomatosis with RCC-HLRCC) due to mutations in the Fumarate Hydratase (FH) gene which inactivate the gene leading to generation of a pseudo-hypoxic state characterized by the upregulation of hypoxia inducible factor (HIF) similar to that seen in the VHL pathway in clear cell RCCC, albeit by a different mechanism (Isaacs, Jung et al. 2005).

The mechanisms underlying chromophobe histology are lesser understood, although an autosomal dominant hereditary cancer syndrome, Birt-Hogg-Dube (BHD) syndrome associated with bilateral multifocal chromophobe RCC is the result of loss of folliculin protein is thought to interact with cellular activate mitogen protein kinase (cAMP) and m-TOR pathways (Nickerson, Warren et al. 2002). Apart from this mechanism, other mechanisms such as upregulation of cellular proto-oncogenic receptor tyrosine kinase (c-KIT) have also been observed in chromophobe RCC (Yamazaki, Sakamoto et al. 2003).

1.2 Clinical experience with VEGF axis inhibition in non clear cell histology

The underlying differences in molecular mechanisms for developing non clear RCC has a potential impact in therapeutic targeting, which resulted in excluding these histologies in the pivotal trials that targeted the VEGF axis with clear cell histology. However, with limitations there is some clinical evidence available indicative of efficacy for VEGF targeting in non clear cell RCC.

The Advanced Renal Cell Carcinoma Sorafenib Expanded Access Program, a non-randomized open label program initiated prior to drug approval treated 158 metastatic papillary RCC patients with sorafenib (Stadler, Figlin et al.). Stable disease was observed in 87 patients of 107 evaluable patients for 8 weeks with a partial response observed in an additional three patients.

In a multi-center, international, non-randomized open label compassionate use trial with sunitinib in poor prognosis populations that were excluded from other trials on the basis of brain metastasis, non clear cell histology, poor performance status and increased age, the overall survival of patients with non clear cell histology was observed to be improved (13.4 months compared to a historical control of 9.4 months) with an overall response rate of 11% for non clear histology (Gore, Szczylik et al. 2009).

Other small retrospective series have reported variable efficacy with sunitinib and sorafenib (Choueiri, Plantade et al. 2008) in patients with metastatic non clear histology with response rates ranging between 5% and 17% while recently a lack of response to sunitinib in 23 patients with metastatic papillary RCC was observed (Plimack E. et al. 2010 J Clin Oncol 28: 15s, 2010 (suppl; abstr 4604)) in a small phase II trial with a best response of 1.6 months in 8 patients demonstrating stable disease.

1.3 Clinical Experience with non VEGF axis inhibition strategies

Experience with non-VEGF axis directed drugs in non clear RCC has also been limited. In the Global Advanced RCC trial comparing temsirolimus, interferon or both for advanced

RCC, (Hudes, Carducci et al. 2007) 124 subjects (20%) had non clear RCC histology. In an exploratory analysis hazard ratios for over all survival among non clear RCC patients favored treatment with temsirolimus compared to interferon or observation. A prospective phase II trial of everolimus in advanced papillary RCC is currently ongoing in Europe and results remain unknown. A new novel oral receptor tyrosine kinase inhibitor, foretinib (formerly known as GSK 1363089/XL880) that targets c-MET and VEGFR-2 has been evaluated in an efficacy trial in advanced papillary RCC with interim data on the first 60 patients recently reported in abstract form (SrinivasinR, et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 5103)). Of the 35 evaluable pts, 4 patients had confirmed partial response and 27 had stable disease as best response with 6 patients ≥12 months, 3 patients ≥ 9 months and 3 patients ≥ 6 months. Four of 5 patients with Hereditary Papillary RCC had shrinkage (15-53%) in all measurable tumors while twenty-three patients with sporadic Papillary RCC had shrinkage (2-58%) in the sum of measurable tumors.
Other trials with single agent erlotinib in advanced stage papillary RCC (Gordon, Hussey et al. 2009) or in combination with bevacizumab are currently underway at the National Institute of Health.

Cytotoxic chemotherapy has so far yielded poor efficacy results in non-clear-cell renal cell carcinoma (RCC). A phase II study conducted to assess the efficacy of carboplatin and paclitaxel in such patients observed a response rate of 0% with a median survival of 63 weeks (Bylow, Atkins et al. 2009). In another phase II multi-center trial that tested gemcitabine and cisplatin in collecting duct tumors in 23 patients found a response rate of 26% with a progression free survival of 7.1 months (compared to historical controls) and an overall survival of 10.5 months with considerable toxicity (Oudard, Banu et al. 2007).

1.4 Mayo Clinic Nephrectomy database experience with non clear cell renal cell cancer

At the Mayo Clinic (Rochester), (Department of Urology) an active kidney tumor registry has been maintained since 1970. The Nephrectomy Registry is currently complete with clinical follow up through 2007 and provides a rich source of clinical outcomes based on various histological subtypes. Between 1970 and 2007, 3714 nephrectomies for RCC were performed that had a specific RCC histo-path subtype with a breakdown as follows:

3051 clear cell RCC

499 papillary RCC

156 chromophobe RCC

8 collecting duct RCC

(Sarcomatoid differentiation can arise in all of these subtypes and is not considered a separate subtype according to the AJCC classification)

Among the 663 nephrectomies for non-clear cell RCC, 26 were M1 at nephrectomy and 48 subsequently developed metastases sometime following nephrectomy. For the 74 cases with distant metastases either at nephrectomy or following nephrectomy, the overall survival rates at 1, 3, and 5 years following distant metastases were 55.2%, 24.9%, and 16.3%, respectively (Leibovich, Lohse et al.). Non-clear cell metastatic RCC survival

reported from another large kidney cancer database from Memorial Sloan Kettering, published by Motzer et al (Motzer, Bacik et al. 2002) also provides insight into the poor prognosis of these histological subtypes. Of the 64 patients followed between 1985 and 2001, the median survival of metastatic non clear cell RCC was found to be 9.4 months, with survival longer for patients with chromophobe tumors than with collecting duct and papillary cancers. Patients in this review had received cytokine and or hormonal treatments with negligible responses highlighting an unmet need for the treatment in this group of patients.

Mayo Clinic (Rochester) annually averages 4-6 metastatic non-clear cell RCCs that undergo nephrectomy with a similar incidence at Mayo Clinic, Florida and Arizona. In addition in the Medical Oncology division at Rochester between 3 and 7 metastatic non-clear cell RCCs are treated annually.

Since the role of active treatment agents in metastatic RCC of non-clear-cell histologies remains to be established and the efficacy of pazopanib in delaying disease progression in metastatic clear cell RCC is unknown in non clear cell histological sub types, the current prospective phase II trial is designed to evaluate the efficacy of pazopanib in advanced stage non clear RCC patients.

1.5 Pazopanib Information

Angiogenesis, the process of new blood vessel formation, plays an important role in the development of malignancy as well as the growth and progression of metastatic lesions. The molecular pathways involved in angiogenesis have been targeted for anti-tumor therapy. Numerous growth factors and cytokines are involved in the angiogenic process. Among these factors, vascular endothelial growth factor (VEGF) has a predominant role as a central mediator of tumor-related angiogenesis, and its expression has been shown to be an adverse prognostic factor for a number of solid tumors [Folkman, 1971; Folkman 1997; Ferrara, 1997].

αβ
GW786034 (pazopanib) is an orally-bioavailable, adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)- α and - β, and stem cell growth factor receptor (c-Kit) [Kumar, 2007]. Pazopanib administered as oral doses up to 800 mg daily is being developed for the treatment of a variety of cancers and is currently approved by the Food and Drug Administration (FDA; New Drug Application #022465), European Medicines Agency (EMA) and other regulatory authorities as a monotherapy treatment for patients with advanced renal cell carcinoma (RCC) and advanced soft tissue sarcoma (STS). GW786034 is hereafter referred to as pazopanib in this document.

Nonclinical pharmacology studies conducted in vitro and in vivo have shown that pazopanib is a potent and selective orally bioavailable, adenosine triphosphate competitive, TKI of VEGFR-1, -2, and -3; PDGFR- α and - β; and c-Kit. Pazopanib was generally efficacious in oral dosing xenograft models and in angiogenesis and neovascularization models using oral and topical (skin and ocular dosing) administration.

As of 09 September 2015, a total of 53 GlaxoSmithKline (GSK)-sponsored studies of pazopanib have been conducted in oncology indications (including 2 studies initiated by

National Cancer Institute [NCI] VEG110827/NCI8063 and PZP114411/ADVL0815). There is 1 ongoing clinical study in Hereditary Hemorrhagic Telangiectasia (HHT). Ten GSK-sponsored studies have been conducted in ophthalmic indications, and 1 GSKsponsored study has been conducted in subjects with psoriasis.

Cumulatively, as of 09 September 2015, approximately 8557 patients and healthy volunteers were enrolled and treated in pazopanib clinical studies, of whom 5909 received pazopanib as monotherapy or in combination with other hemotherapeutic agents. Data collected to date show that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings.

In VEG110727 (a randomized placebo-controlled Phase III study of pazopanib monotherapy in subjects with STS), the median time on pazopanib was 19.4 weeks, as compared with 8.1 weeks in the placebo arm. The most common AEs (≥20%) reported in the pazopanib arm (as of 29 Mar 2013) were fatigue (65%), diarrhea (59%), nausea (56%), weight decreased (51%), hypertension (42%), decreased appetite (40%), hair color changes (39%), vomiting (34%), tumor pain (30%), dysguesia (28%), gastrointestinal pain (24%), headache (24%), musculoskeletal pain (23%), myalgia (23%), and dyspnea (20%). Twenty-eight percent of subjects on placebo and 63% of subjects on pazopanib experienced an AE of maximum Grade 3 or higher. The proportion of subjects who experienced maximum Grade 4 and Grade 5 AEs was similar in both treatment arms.
In VEG110655 (a randomized, placebo-controlled, Phase III study of pazopanib monotherapy in subjects with ovarian, fallopian tube or primary peritoneal cancer), the mean time on study drug in the pazopanib arm was shorter than in the placebo arm (8.9 months vs. 11.7 months). The most common AEs (>20%) occurring in subjects in the pazopanib arm included hypertension (54%), diarrhea (53%), nausea (37%), headache (29%), fatigue (28%), and neutropenia (22%). A higher proportion of subjects in the pazopanib arm had Grade 3 or Grade 4 AEs compared with the placebo arm (63% vs. 23%); the majority of these events were Grade 3. The most common Grade 3 AEs (≥5%) in the pazopanib arm included hypertension (29%), diarrhea (8%), neutropenia (6%) and ALT increased (5%). Fatal SAEs were reported in 3 subjects in the pazopanib arm and 1 subject in the placebo arm.

An analysis of integrated safety data from VEG110655 and VEG114012 (a randomized, placebo-controlled, Phase II study of pazopanib monotherapy in East Asian women with ovarian, fallopian tube or primary peritoneal cancer) showed a safety profile similar to that observed in the pazopanib arm of VEG110655 alone. Adverse events that occurred in at least 20% of pazopanib-treated subjects in the integrated analysis included: hypertension (57%), diarrhea (52%), nausea (34%), fatigue (27%), headache (27%), neutropenia (27%), hair color changes (23%), and ALT increased (20%). Of the most common AEs in pazopanib-treated subjects, the incidences of diarrhea, nausea, and fatigue in the ovarian studies were similar or lower compared with those in the integrated STS and RCC studies, as well as in RCC Study VEG108844. Hypertension and neutropenia occurred more frequently in pazopanib-treated subjects in the ovarian studies.

A number of these events are known class effects of VEGF inhibitors. Therefore, this protocol is designed to closely monitor and provide clear management guidelines for these events based on the clinical experience with pazopanib to date.

2.0 Goals

2.1 Primary

2.11 To determine the efficacy of pazopanib in non clear cell metastatic renal cell cancer patients as assessed by the overall survival rate at 12 months.

2.2 Secondary

2.21 To determine the rates of best tumor response at the end of the first two treatment cycles of pazopanib in non clear cell metastatic renal cell cancer patients.

2.22 To determine the benefit of pazopanib in increasing progression free survival time.

2.23 To describe toxicity profile of pazopanib in non clear cell metastatic renal cell cancer patients.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years

3.12 Histological confirmation of non-clear cell renal cancer (including Chromophilic (papillary), Chromophobic, Oncocytic, sarcomatoid, Collecting duct (Bellini's duct), translocation-type carcinoma or medullary renal cell carcinoma.

3.13 Up to one prior treatment for metastatic non clear cell carcinoma is allowed prior to registration as long as the agent used to treat was not pazopanib.

3.14 Measurable or non-measurable metastatic disease as defined in Section 11.0.

3.15 ECOG Performance Status (PS) 0, 1 or 2 (Appendix II).

3.16 The following laboratory values obtained ≤ 14 days prior to registration.

- ANC ≥1500
- PLT ≥100,000
- HgB >9.0 g/dL. NOTE: Subjects may not have had a transfusion within 7 days of registration.)
- Total Bilirubin <1.5 x ULN
- Alanine amino transferase (ALT) ≤2.5 X ULN. NOTE: Concomitant elevations in bilirubin and ALT above 1.0 x ULN (upper limit of normal) is not permitted.

- Aspartate aminotransferase (AST) ≤2.5 X ULN. Note: Concomitant elevations in bilirubin and AST above 1.0 x ULN (upper limit of normal) is not permitted.
- Urine Protein to Creatinine Ratio (UPC; appropriate appendix) (UPC) <1 NOTE: If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.
- Prothrombin time (PT) or international normalized ratio (INR) ≤1.2 X ULN NOTE: Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation

3.17 A female is eligible to enter and participate in this study if she is of:

a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:
   - A hysterectomy
   - A bilateral oophorectomy (ovariectomy)
   - A bilateral tubal ligation
   - Is post-menopausal

   Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

   Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

b. Childbearing potential, including any female who has had a negative serum pregnancy test, ≤7 days prior to registration.
c. Agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:
   - Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product
   - Oral contraceptive, either combined or progestogen alone
   - Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year
   - Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject
   - Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)

3.18 Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

3.19 Willing to return to Mayo Clinic enrolling institution for follow-up.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown
- Nursing women
- Pregnant women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive.

3.24 Prior history of receiving pazopanib treatments.

3.25 Uncontrolled intercurrent illness including, but not limited to:
- ongoing or active infection,
- symptomatic anemia, uncontrolled hypertension hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].,
- symptomatic congestive heart failure as defined by the New York Heart Association (NYHA) (See Appendix IV), Does not exclude Class III CHF.
- previously treated with therapies that are known to negatively impact cardiac function (e.g. prior treatment with anthracyclines)
- unstable angina pectoris,
- cardiac arrhythmia,
- evidence of active bleeding or bleeding diathesis
- psychiatric illness/social situations that would limit compliance with study requirements,
- or any other serious uncontrolled medical disorders in the opinion of the investigator.

3.26 History of cerebrovascular accident including transient ischemic attack (TIA), myocardial infarction, pulmonary embolism or untreated deep venous thrombosis (DVT), Coronary artery bypass graft surgery within 6 months prior to registration.

Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible

3.27 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.28 Other active malignancy ≤5 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.29a History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

3.29b Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

- Active peptic ulcer disease
- Known intraluminal metastatic lesion/s with risk of bleeding
- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess ≤28 days prior to registration.
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
- Malabsorption syndrome
- Major resection of the stomach or small bowel.

3.29c Corrected QT interval (QTc) > 480 msecs using Bazett's formula.

3.29d Receiving any medications or substances with risk of torsades de pointes (see Appendix II). Note: medications or substances on the list "Drugs with Risk of Torsades de Pointes" are prohibited. Medications or substances on the list "Drugs with Possible or Conditional Risk of Torsades de Pointes" may be used while on study with extreme caution and careful monitoring.

3.29e Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels and/or hemoptysis in excess of 2.5 mL (or one half teaspoon) ≤8 weeks of registration

3.29f Treatment with any of the following anti-cancer therapies: radiation therapy, surgery or tumor embolization, chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy ≤ 14 days prior to registration.

3.39g Prior autologous or allogeneic organ or tissue transplantation.

3.39h Elective or planned major surgery to be performed during the course of

the trial.

3.39i Receiving any medications or substances that are **strong or moderate inhibitors** of CYP3A4 (for a listing of medications or substances see Appendix VI).

Use of the following strong or moderate inhibitors are prohibited ≤ 7 days prior to registration.

3.39j Receiving any medications or substances that are **inducers** of CYP3A4 (for a listing of medications or substances see Appendix VI).
Use of inducers are prohibited ≤ 7 days prior to registration.

4.0 Test Schedule **Tests and procedures**	Active Monitoring Phase					
	≤28 days prior to registration	≤14 days prior to registration	Day 1[4], Every cycle	On interval weeks 2, 6, 10	Every other cycle	End of treatment
Informed Consent	X					
History and exam, Wt, PS			X			X
Adverse event assessment			X			
Height		X				
Pregnancy test		X[2]				
Vital Signs, including temperature		X	X			X
Echo (2D M-Mode)	X[R]				X[8]	
Hematology CBC with diff, platelets		X	X[R,6]			X
Chemistries[1]		X	X[R,6]	X[9]		X
UPC Urine		X				
Thyroid Function Test (TSH)		X[R]			X[R]	
Coagulation Test: PT, PTT		X	X			
CT Head/MRI		X[R]				
CT scan of chest, abdomen or pelvis, MRI, etc		X[R]			X[7]	
Bone Scan					X[5]	
EKG		X[R]	X			
Medication Diary			X[3]			

1. SGOT, SGPT, total bili, Na, K, CI, CO_2, BUN, creatinine, LDH, hemoglobin, calcium, albumin, total protein, magnesium, phosphorus and alkaline phosphatase.
2. For women of childbearing potential, ≤7 days prior to registration.
3. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
4. +/- 3 days
5. If applicable
6. Research funded, cycles 1 and 2 only
7. Use the same method throughout the study. Follow-up scans to be performed every other cycle (8 weeks). Repeat measurements are required 8 weeks following an objective Response. See Section 11.0 for full RECIST criteria.
8. Every 4 months while on study, sooner should clinical symptoms indicate. These follow-up echocardiograms will coincide with restaging visits.
9. SGOT, SGPT, total bili, only and can be done at study site or locally and faxed.

R Research funded (see Section 19.0)

5.0 Stratification / Grouping Factor: None.

6.0 Registration Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Prior to accepting the registration, registration application will verify the following:
- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for unspecified future research of renal cancer at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future

research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.
- Patient has given permission to store and use his/her samples for the mandatory future banking(section 14.1)

6.5 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.6 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.8 Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Arizona, or Mayo Clinic Florida under the supervision of a medical oncologist who confirms the patient is a suitable candidate for this study.

6.9a Study drug is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose Level	Route	Day
Pazopanib	800 mg	PO	once daily

Cycle length=28 days

Protocol treatment consists of four 200mg tablets (800 mg) of pazopanib by mouth once a day.

7.13 GW786034

Pazopanib monohydrochloride salt is supplied as aqueous film-coated tablets containing 200 mg of the free base. The 200-mg tablets are oval-shaped and gray in color. Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.

Pazopanib will be provided to the sites by Novartis. The 200-mg pazopanib tablets are packaged 34 to a bottle. Bottles are made of high-density polyethylene and have a child-resistant closure. Each bottle will be labeled with the protocol number, dosing and storage instructions, sponsor name and address, and the expiration date, when required. The contents of the label will be in accordance with all applicable regulatory requirements.

7.12 Dosage and Administration

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in area under the plasma drug concentration curve (AUC) and maximum observed plasma drug concentration (C_{max}).

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant.

If a dose is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking pazopanib, the subject should not take a replacement dose on that day. The subject should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, the subject should be instructed to notify the investigator.

As a general rule, if dose reduction of pazopanib is necessary, the dose should be reduced stepwise by 200 mg at each step, and the subject should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the medication may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

If a subject's treatment has been interrupted for more than 21 days, the Investigator must contact the Study Physician to review the subject's condition in order to resume the treatment.

7.2 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 For this protocol, the patient must return to Mayo Rochester, Florida, or Arizona for evaluation at least every 28 days (+/- 3 days).

7.4 Criteria for Treatment Discontinuation

- Patients who develop PD/recurrent disease while receiving therapy at the time of response assessments will be discontinued from active study treatment and go off protocol;
- Grade 3 or 4 toxicity requiring break from treatment and inability to re-initiate treatments with a ≥28 day delay;
- Completion of 12 months of therapy.

8.0 Dosage Modification Based on Adverse Events

8.1 Pazopanib

8.11 Pazopanib Dose Reduction Levels

Starting Dose	800 mg once daily
Dose Level -1	600 mg once daily
Dose Level -2	400 mg once daily

8.12

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT			
Investigations	Platelet count decreased Grade 3 or 4	Pazopanib	Omit until ≤ 2 then restart at next lower dose level. If no recovery to grade 2, discontinue
Investigations	Electrocardiogram QT corrected interval prolonged ≥ 500msec Grade 3	Pazopanib	Discontinue pazopanib
Renal and urinary disorders	Creatinine ≥Grade 3	Pazopanib	Omit until < 3 then restart at next lower dose level. If ≥ 3 recurs, reduce one dose level again until no dose can be given

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Vascular disorders	Thromboembolic event DVT/PE Grade 3 Grade 4 Arterial Thrombosis/Ischemia Any Grade	Pazopanib	Omit and initiate anticoagulant. Restart at reduced dose if • Subject must have been treated at desired level of anticoagulation for at least 1 week • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Note: When treating with warfarin, INR S/B monitored within 3 to 5 days after any change in pazopanib dosing and then at least weekly until INR is stable. The dose of warfarin may need to be adjusted to maintain the desired level of anticoagulation. Discontinue pazopanib Discontinue pazopanib
Vascular disorders	Hypertension	Pazopanib	See table 8.2
Gastrointestinal disorders	Any GI bleed Grade 2-4	Pazopanib	Discontinue pazopanib
Respiratory, thoracic and mediastinal disorders	Any Pulmonary bleed Grade 2-4	Pazopanib	Discontinue pazopanib
Dermatology/ Skin	Dermatitis Grade 2 skin changes w/pain, limiting ADL's Grade3 severe skin changes w/pain Limiting self care ADL's	Pazopanib	Omit until ≤ 1, then restart at next lower dose level. If recurrent, reduce by another dose level or discontinue Discontinue

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
All Other	Grade 2 or 3, if clinically significant Grade 4	Pazopanib	Omit until ≤ 1 Discontinue Pazopanib

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.2 Pazopanib-at time of retreatment

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
AT TIME OF RETREATMENT			
Investigations	Platelet count decreased Grade 3 or 4	Pazopanib	Hold until ≤ 2 then restart at next lower dose level. If no recovery to grade 2, discontinue
Investigations	Electrocardiogram QT corrected interval prolonged ≥ 500msec Grade 3	Pazopanib	Discontinue pazopanib
Renal and urinary disorders	Creatinine > Grade 3	Pazopanib	Hold until < 3 then restart at next lower dose level. If ≥ 3 recurs, dose reduce again until no dose can be given

➔ ➔ ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** 🡐 🡐			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Vascular disorders	Thromboembolic event DVT/PE Grade 3	Pazopanib	Hold and initiate anticoagulant. Decrease 1 dose level if • Subject must have been treated at desired level of anticoagulation for at least 1 week • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Note: When treating with warfarin, INR S/B monitored within 3 to 5 days after any change in pazopanib dosing and then at least weekly until INR is stable. The dose of warfarin may need to be adjusted to maintain the desired level of anticoagulation.
	Grade 4		Discontinue pazopanib
	Arterial Thrombosis/Ischemia Any Grade		Discontinue pazopanib
Vascular disorders	Hypertension	Pazopanib	See table 8.3
Gastrointestinal disorders	Any GI bleed Grade 2-4	Pazopanib	Discontinue pazopanib
Respiratory, thoracic and mediastinal disorders	Any Pulmonary bleed Grade 2-4	Pazopanib	Discontinue pazopanib
Dermatology/ Skin	Dermatitis Grade 2 skin changes w/pain, limiting ADL's	Pazopanib	Hold until ≤ 1, then restart at next lower dose level. If recurrent. reduce by another dose level or discontinue
	Grade3 severe skin changes w/pain Limiting self care ADL's		Discontinue

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
All Other	Grade 2 or 3, if clinically significant Grade 4	Pazopanib	Hold until ≤ 1 Discontinue pazopanib

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.3 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
Scenario A) • Asymptomatic and persistent[d] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	• Continue pazopanib treatment at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlledb BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or • Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Interrupt pazopanib treatment if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled[e], restart pazopanib treatment reduced by one dose level
• Symptomatic[f] hypertension or • Persistent[g] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Interrupt pazopanib treatment • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended • Once BP is well controlled, restart pazopanib treatment **reduced by one dose level**

Refractory hypertension unresponsive to above interventions.	• Permanently discontinue pazopanib treatment • Continue follow-up per protocol.
LVEF-drop (%) or CTCAE grade	**Action and Dose Modification**
Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN OR LVEF drop >15% from baseline regardless of whether value is below institution's LLN.	• Interrupt pazopanib study treatment and repeat ECHO within 2 weeks[b] and monitor and control BP. • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) o Restart study treatment[f] reduced by one dose level *(Please consult with Novartis if there are any questions prior to restarting)* o Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; monitor BP; continue in intervals of 12 weeks thereafter • If repeat LVEF does not recover within 4 weeks o Consult with cardiologist o **Permanently discontinue pazopanib treatment Repeat ECHO after 2, 4, 8, 12, and 16 weeks or un**til resolution *Please Consult with Novartisif there are any questions*
Symptomatic[c:] Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	• **Permanently discontinue pazopanib treatment** • **Consult with cardiologist** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
Symptomatic[c] Grade 4: resting LVEF <20%	
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs. REFER READER TO ECG SECTION IN PROTOCOL	
QTc ≥ 480 < 500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥500 msec	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt pazopanib. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC ≥3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2. Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	

Grade 1	For hemoptysis, interrupt pazopanib and contact the Novartis Study Physician to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ Grade 1. Step 2. Restart pazopanib ; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt pazopanib . Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib dosing (eg, re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue pazopanib with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 2.

	Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IP and follow-up per protocol.
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue pazopanib at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold pazopanib 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart pazopanib with a dose reduction to dose level -1 (if it was a full dose[800mg]) or one dose lower than the patient was receiving prior to developing the skin changes. 4. If recurrent consider a further dose reduction by 1 dose level until dose level -2. If patient has a Grade 2 toxicity on dose level -2, then consider stopping the drug.
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue pazopanib
Other Clinically Significant Adverse Events[a]	
Grade 1	Continue pazopanib ; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart pazopanib dose-reduced by 200 mg(1 dose level) and monitor as clinically indicated.
Grade 4	Discontinue pazopanib and continue follow-up per protocol.

a. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v3)
b. If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.
c. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d. Hypertension detected in two separate readings during up to three consecutive visits
e. Well-controlled blood pressure defined as SBP <140 mm Hg and DBP <90 mm Hg in two separate readings during up to three consecutive visits.
f. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.
g. Persistent hypertension is defined as asymptomatic hypertension after initially successful anti-hypertensive intervention.

8.4 Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[0] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[0] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria[0]:** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the subject is benefiting from the study treatment, contact Novartis Study Physician for possible re-challenge. Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. **Recurrence – Liver Event Stopping Criteria[0]:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. At the time of the recurrence, complete the eCRF liver event forms.

Event	Dose Modification Algorithms
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[0] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria[0]:** (1) Discontinue pazopanib immediately, report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence , and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist, collect PK sample and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging -Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs [a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin[0] elevation without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury.. (2) If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.
c. When a liver chemistry event meets the Liver Event Interruption Criteria, or Liver Event Stopping Criteria, blood samples should be obtained for PK and for clinical laboratory testing by the central laboratory (Liver Event Kits will be provided for this purpose).

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; eCRF electronic case report form; IP investigational product; LFT liver function tests; PK pharmacokinetics; SAE serious adverse event; ULN upper limit of normal

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-

Based, Clinical Practice Guidelines. J Clin Oncol Vol 24, No 19 (July 1), 2006: pp. 3187-3205

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). If grade 2 diarrhea consider dose reduction of pazopanib. If grade 2 diarrhea persists after 48 hours total treatment with loperamide discontinue pazopanib.

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

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

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **Special Situations for Expedited Reporting**

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/Symptoms	CTCAE Grade at which the event will not be expeditedly reported.[1]
Gastrointestinal disorders	Abdominal pain	Grade 3
	Diarrhea	Grade 3
	Nausea	Grade 3
	Vomiting	Grade 3
General disorders and administrations site conditions	Fatigue	Grade 3
Metabolism and nutrition disorders	Anorexia	Grade 3
Nervous system disorders	Headache	Grade 3
Skin and subcutaneous tissue disorders	Hair color changes	Grade 3
Vascular disorders	Hypertension	Grade 3

[1]These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed

Specific protocol exceptions to expedited reporting will be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.32 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.33 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- **Reportable categories of Death**
    - Death attributable to a CTCAE term.

- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benigh, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.34 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.35 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.4 Expedited Reporting Requirements for IND/IDE Agents

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

[redacted]

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC IND Coordinator to determine if FDA submission is needed, and to the MCCC SAE Coordinator.

NOTE: The Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form is not being used for investigational agent(s) in this study.

10.5 Reporting requirements for Novartis

All Events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English..

10.51 Serious adverse event reporting

All serious adverse events must be reported by facsimile within 24 hours to the oncology Novartis DS&E department with the appropriate fax coversheet (see Appendix IX). Fax: [redacted]

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) ***(For patients taking Pazopanib / Novartis drugs)***.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring

- after the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

All Events must be reported to Novartis within 24 hours of learning of its occurrence Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form by fax to (fax: [redacted] within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets**.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Pazopanib Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 weeks	Pregnancy Notification Form	2 weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT: >3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) **or with** hypersensitivity symptoms (e.g., fever, rash).	24 hours	SAE data collection tool. [b]Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. [b]Updated Liver Event CRF
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	24 hours	SAE data collection tool. Liver Event CRF[b]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[b]

a. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.
b. Liver event documents should be completed as soon as possible.

SAEs brought to the attention of the investigator at any time after cessation of pazopanib and considered by the investigator to be related or possibly related to pazopanib must be reported to Novartis if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

10.6 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal Disorders	Baseline number of stools per day	X	
	Diarrhea		X
Vascular Disorders	Hypertension	X	X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Blood bilirubin increased	X	X
	Lymphocytes decreased	X	X
Metabolism and Nutrition Disorders	Hypophosphatemia	X	X
	Hyponatremia	X	X
	Hypomagnesemia	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6.

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

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) guidelines (version 1.1) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- 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.

- 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. The lesions should be measured on the same pulse sequence. 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: 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.

- 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 scans are preferable.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ 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:

        i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

        ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

        iii 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, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

- 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.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen

but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Prior treatment for metastatic non clear cell renal cell cancer: none vs. sorafenib vs. sunitinib vs. temsirolimus vs. interferon vs bevacizumab vs everolimus vs. other metastatic renal cell cancer treatments.

12.2 Non-clear cell metastatic renal cell cancer histology: chromophilic vs. chromophobic vs. oncocytic vs. collecting duct vs. sarcomatoid differentiation.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 Patients who develop non-CNS PD at any time should go to event monitoring.

13.5 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

14.0 Body Fluid Biospecimens

Note: As of addendum 7 all blood and urine correlatives discussed in section 14 are no longer being collected at any of the Mayo Clinic sites. All blood and urine specimens collected prior to the implementation of addendum 7 will be stored and utilized in the manner described above if and when funding becomes available.

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol*

Correlative Study	Mandatory or Optional	Specimen to Collect	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to collect)	Prior to Registration (≤14 days)	Cycle 3 Day 1	Cycle 5 Day 1	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Bank for Future Proteomics, Metabolomics, and Genomics Studies (Section 14.21)	Mandatory	Whole Blood	EDTA (purple top)	4, 6 mL (2)	X	X	X	No	Frozen / Dry Ice
Bank for Future Proteomics, Metabolomics, and Genomics Studies (Section 14.21)	Mandatory	Whole Blood	Sodium Citrate (blue top)	5 mL (1)	X	X	X	No	Frozen / Dry Ice
Bank for Future Proteomics, Metabolomics, and Genomics Studies (Section 14.22)	Mandatory	Whole Blood	SST (black/red top)	8.5 mL (1)	X	X	X	No	Frozen / Dry Ice
Bank for Future Proteomics, Metabolomics, and Genomics Studies (Section 14.23)	Mandatory	Whole Blood	Paxgene	5 mL (1)	X	X	X	No	Frozen / Dry Ice
Bank for Future Proteomics, Metabolomics, and Genomics Studies (Section 14.24)	Mandatory	Urine	-	10-15 mL	X	X	X	No	Frozen / Dry Ice

*Research Blood and Body fluid specimens are funded by Mayo

14.2 Collection and Processing

Mayo Clinic Florida and Mayo Clinic Arizona will collect and ship all samples to Mayo Clinic Rochester for processing.

14.21 Please include the following tissue reports with specimens: Research Blood Submission Form and Research Urine Submission Form.

14.22 EDTA and Sodium Citrate Whole Blood

Collect at the following time points:

Prior to Registration (≤14 days)
Cycle 3 Day 1 (Prior to Treatment)
Cycle 5 Day 1 (Prior to Treatment)

Collect the following tubes of blood:
Two 5mL EDTA (purple top) tube
One Sodium Citrate (blue top) tube

Process whole blood as follows:
Centrifuge EDTA and Sodium Citrate tubes at 600g for 10 minutes

Label all cryovials with Protocol #, Patient Initials and Patient ID #, Type of Sample (EDTA plasma (4), Sodium Citrate plasma (2), EDTA buffy coat (2), Sodium Citrate buffy coat (1)).

Divide plasma from each blood tube into two cryovials, approximately 1.25 mL of plasma per tube (6 aliquots- 4 EDTA plasma and 2 Sodium Citrate aliquots).

Aliquot buffy coat from each tube into separate Cryovials.

Label two of each of the EDTA and one of the Sodium Citrate plasma aliquots PRP (Platelet Rich Plasma). Then aliquot 0.5mL of each of these aliquots into 2 cyrovials (labeled EDTA PRP plasma and Sodium Citrate PRP plasma). In addition label the new aliquots with Protocol #,, Patient Initials and Patient ID #, Date of Birth, and U1806.

Label the second set of EDTA and Sodium Citrate aliquots with PPP (Platelet Poor Plasma). Add 50 uL of protease inhibitor cocktail / mL of plase to each of these cryovials and mix.Centrifuge cryovials at 9000g for 5 minute to separate the platelets. Aliquot 0.5 mL of each sample into two cryovials and label with sample type (2 cryovials for EDTA PPP plasma and 2 cryovials with Sodium Citrate PPP plasma). In addition label the new aliquots with Protocol #, Patient Initials and Patient ID #, Date of Birth and U1806.

Snap freeze all aliquots (4 PRP EDTA aliquots, 2 PPP EDTA aliquots, 2 PRP Sodium Citrate aliquots, 2 PPP Sodium Citrate aliquots, 2 EDTA buffy coat, 1 Sodium Citrate buffy coat aliquot)

Store at -80C until requested.

14.23 SST Tubes of Whole Blood

Collect at the following time points:

Prior to Registration (≤14 days)
Cycle 3 Day 1 (Prior to Treatment)
Cycle 5 Day 1 (Prior to Treatment)

Collect the following tubes of blood:
One 8.5mL SST (black/red top) tube

Process whole blood as follows:
Centrifuge SST tube at 600g for 10 minutes.

Aliquot the serum equally between two 2mL cryovials.

Re-aliquot one of the serum tubes into 0.5 mL aliquots (~4 serum aliquots). Label the new serum aliquots with Protocol #, Patient Initials and Patient ID #, Date of Birth, U1806, and **Serum w/o inhibitor.**

With second 2mL aliquot of serum add 50 uL protease inhibitor cocktail / mL of serum and mix. Aliquot 0.50 mL of this serum into cryovials (~4 serum aliquots). Label the new serum aliquots with Protocol #, Patient Initials and Patient ID #, Date of Birth, and U1806, and **Serum w/ inhibitor**.

Store at -80C until requested.

14.24 PAXgene RNA

Collect at the following time points:

Prior to Registration (≤14 days)
Cycle 3 Day 1 (Prior to Treatment)
Cycle 5 Day 1 (Prior to Treatment)

Collect the following tubes of blood:
One 5mL Paxgene tube

Process whole blood per manufacturer's instructions (as follows):

Incubate blood sample for at least 2 hours at room temp to ensure cells are lysed.

Centrifuge tube for 10 minutes at 3000-5000 x g using a swing out rotor **NOTE: Tubes may break if tube adapters for round bottom tubes is not used.**

Pipet off the supernatant and discard.

Add 4mL RNase-free water to the pellet and close tube with a fresh secondary BD Hemogard closure.

Vortex the pellet until visible dissolved and centrifuge at 3000-5000 x g using a swing-out rotor.

Decant or Pipet off the supernatant and discard. **NOTE: Be sure to remove as much supernatant as possible. Remaining supernatant will inhibit lysis and dilute the lysate, thus affecting binding of RNA to PAXgene membrane.**

Add 350µL Buffer BR1, and vortex until pellet is visibly dissolved.

Pipet sample into 1.5mL microcentrifuge tube and add 300µL Buffer BR2 and 40µL proteinase K. **NOTE: Do not mix Buffer BR2 and proteinase K together prior to adding to sample.**

Mix by vortexing for 5 seconds, and incubate on a shaker (400-1400 rpm) for 10 minutes at 55ºC.

Pipet lysate into PAXgene Shredder spin Column (lilac) and place in a 2mL processing tube. Centrifuge for 3 minutes at maximum speed (but not greater than 20,000 x g)
NOTE: Be sure that the all the lysate is transferred to the spin column.
NOTE: Some samples may flow through spin column without being centrifuged.

Transfer the supernatant that flowed through column into a fresh 1.5mL microcentrifuge tube without disturbing the pellet in the processing tube.

Add 350uL ethanol (96-100%) and mix by vortexing. Centrifuge briefly (1-2 seconds at 500-1000- x g) to remove drops from the sides of the tube. **NOTE: Do not centrifuge longer or RNA yield will be compromised.**

Pipet 700µL sample into PAXgene RNA spin column (red) and place in a 2mL processing tube. Centrifuge for 1 minute at 8000-20,000 x g.

Place the spin column in a new 2mL processing tube and discard the old processing containing flow-through.

Pipet remaining sample into the PAXgene RNA spin column, and centrifuge for 1 minute at 8000-20,000 x g. Place the spin column in a new 2mL processing tube and discard the old processing tube containing the flow-through.
NOTE: Carefully pipet the sample into the spin column and visually check that the sample is completely transferred to the spin column.

Pipet 350µL Buffer BR3 into the PAXgene RNA spin column, and centrifuge for 1 minute at 8000-20,000 x g. Place the spin column in a new 2 mL processing tube and discard the old processing tube containing the flow-through.

Add 10µL DNase I stock solution to 70uL Buffer RDD in a 1.5mL microcentrifuge tube, and mix by gently flicking the tube, and centrifuge to collect liquid at the bottom of tube.
NOTE: DNase I is especially sensitive to denaturation. Mix ONLY by gently flicking the tube. DO NOT VORTEX.

Pipet the DNase I incubation mix (80µ) directly onto the PAXgene RNA spin column membrane, and let sit at room temperature for 15 minutes. NOTE: Be sure DNase I incubation mix is placed directly onto the membrane (not on walls or the O-ring of the spin column).

Pipet 350µL Buffer BR3 into the PAXgene RNA spin column, and centrifuge for 1 minute at 8000-20,000 x g. Place the spin column in a new 2 mL processing tube and discard the old processing tube containing flow-through.

Pipet 500µL diluted BR4 Buffer to the PAXgene RNA spin column, and centrifuge for 1 minute 8000-20,000 x g. Place the spin column in a new 2 mL processingtube, and discard the old processing tube and flow-through. **NOTE: Buffer BR4 is supplied as a concentrate and must be diluted with ethanol (96-100%) prior to use. For 500µL for diluted BR4 buffer use 100µL BR4 concentrate and 400 µL ethanol.).**

Add another 500µL diluted BR4 Buffer to the PAXgene spin column, and centrifuge for 3 minutes at 8000-20,000 x g.

Discard the tube containing the flow-through, and place the PAXgene RNA spin column in a new 2mL processing tube, and centrifuge for 1 minute at 8000-20,000 x g.

Discard the tube containing the flow-through, and place the PAXgene RNA spin column in a 1.5mL microcentrifuge tube and pipet 40µL Buffer BR5 directly onto the PAXgene RNA

spin column membrane, and centrifuge for 1 minute at 8000-20,000 x g to elute the RNA. **NOTE: It is important to wet the entire membrane with Buffer BR5 to achieve maximum elution efficiency.**

Repeat the elution step using the same microcentrifuge tube – Pipet 40µL Buffer BR5 directly onto the PAXgene RNA spin column membrane, and centrifuge for 1 minute at 8000-20,000 x g to elute the RNA.

Incubate for 5 minutes at 65º. **NOTE: This step denatures the RNA. Do not exceed the incubation time.**

Chill on ice.

Store at -80C until requested.

14.25 Urine

Mayo Clinic Florida and Mayo Clinic Arizona will collect and ship all samples to Mayo Clinic Rochester for processing.

Collect at the following time points:

Prior to Registration (≤14 days)
Cycle 3 Day 1 (Prior to Treatment)
Cycle 5 Day 1 (Prior to Treatment)

Collect the following:
10-15 mL Urine

Process urine as follows:

Centrifuge 3mL urine at 600g for 10 minutes.

Aliquot 1 mL into two cryovials without disturbing pellet. Label cryovials with Protocol #, Patient Initials, and Date of Birth.

On the first urine cryovial label **Urine w/o Inhibitor**, and set a side.

For the second urine aliquot, add 50 uL / mL and label **Urine w/ Inhibitor.**

Store urine aliquots at -80C until requested.

14.3 Specimen Shipping and Handling

14.31 Collection Supplies

Collection supplies should be provided at each site.

14.32 Shipping and Storage

All specimens must be collected and shipped Monday – Thursday ONLY.

Samples will be stored at -80ºC and consolidated at the end of the study.

Samples will be stored at the following locations:

Mayo Clinic Rochester
[redacted]

Upon request samples will be shipped on dry ice via overnight courier to the appropriate Mayo institution.

14.33 Background and Methodology

Samples will be available for future correlative studies in proteomics, metabolomics, and genomics as they are developed.

Samples will be analyzed at Mayo Rochester upon request.

15.0 Drug Information

15.1 Pazopanib HCl (GW786034, Votrient®)

15.11 **Background**: Pazopanib HCl is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

15.12 **Formulation**: Pazopanib is supplied by Novartis as aqueous film-coated tablets containing 200 mg and 400 mg of the free base. Both 200 mg and 400 mg tablets are oval-shaped, white and packaged in white high density polyethylene (HDPE) bottles with white plastic, induction seal and child-resistant caps. Bottles of 200 mg tablets contain 34 tablets each and bottles of 400 mg tablets contain 68 tablets each.

Tablet excipients in both tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, macrogol/polyethylene glycol 400 and polysorbate 80.

15.13 **Preparation and storage**: The intact bottles should be stored at controlled room temperature [20°C - 25°C (68°F - 77°F)]. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

15.14 **Administration:** The medication is taken orally. Pazopanib should be taken without food, at least 1 hour before or 2 hours after a meal. Pazopanib should be taken whole with water and must not be broken or crushed. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

15.15 **Pharmacokinetic information**:
a) Absorption – Pazopanib is absorbed orally with an absolute oral bioavailability range of 13.5 to 38.9% after an 800 mg dose, with a median absolute bioavailability of 21%. Plasma concentrations of pazopanib peak from 2 to 4 hours following single dose administration. Systemic exposure to pazopanib is increased when administered with food. Administration with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Pazopanib should be administered at least one hour before or 2 hours after a meal. Administration of pazopanib as a crushed tablet increases the rate and extent of oral absorption relative to administration of the whole tablet. The crushing of the tablet increases AUC by 46% and C_{max} by approximately 2-fold, but decreases t_{max} by approximately 2 hours relative to administration of the whole tablet. Consequently, it is recommended not to crush pazopanib tablets.
b) Distribution – Binding of pazopanib to human plasma protein in vivo was greater than 99% with no concentration dependence. Pazopanib is associated with a small volume of distribution (9.2 to 131L).
c) Metabolism – In vitro studies demonstrate pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8. Patients who have AST/ALT >3 X ULN and concurrent bilirubin >2 X ULN must permanently discontinue pazopanib. Use of pazopanib is not recommended in patients with total biblirubin >3 X ULN (regardless of any ALT) due to insufficient data with this severe impairment.
d) Elimination – Pazopanib has a mean half-life of 30.9 hours after administration of an 800mg dose. Elimination is primarily via feces with renal elimination accounting for < 4% of the administered dose.

15.16 **Potential Drug Interactions**: <u>CYP3A4 Inhibitors and Inducers</u>: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., itraconazole, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin, voriconazole, ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Pazopanib should not be used if chronic use of strong CYP3A4 inducers cannot be avoided. Please see Appendix VI for a list of strong inhibitors and inducers of CYP3A4.

CYP Substrates: Results from drug-drug interaction trials conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19. Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for pazopanib or consider discontinuing simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

If the concomitant use of a PPI is medically necessary, the dose of pazopanib should be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2- receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

With concomitant use of pazopanib with lapatinib (an inhibitor of P-gp, BCRP and a weak inhibitor of CYP3A4), patients should be observed for adverse reactions and the pazopanib dose should be reduced as needed.

In vitro studies also showed that pazopanib inhibits UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs eliminated by UGT1A1 and OATP1B1. Coadministration of pazopanib 400 mg once daily with cetuximab 250 mg/m2 and irinotecan 150 mg/m2 resulted in a 20% increase in systemic exposure to SN-38 (a substrate for UGT1A1 and OATP1B1).

15.17 **Known potential toxicities**:

Summary of adverse reactions in patients with renal cell carcinoma (RCC):

Very common: ≥ 1/10 (≥ 10%)

Metabolism and nutrition: Anorexia
Nervous system: Headache
Cardiac: Bradycardia
Vascular: Hypertension
Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting
Hepatobiliary: Increased ALT and AST
Skin and subcutaneous tissue: Hair depigmentation
General: Asthenia, fatigue

Common: ≥1/100 and <1/10 (≥ 1% and <10%)
Blood and lymphatic: Neutropenia, thrombocytopenia
Endocrine: Hypothyroidism
Metabolism and nutrition: Weight decreased
Nervous system: Dysgeusia, transient ischemic attack
Cardiac: Myocardial ischemia, QT prolongation
Vascular: Epistaxis, gastrointestinal hemorrhage, hematuria, venous thromboembolic events
Respiratory, thoracic and mediastinal: Dysphonia
Gastrointestinal: Dyspepsia, lipase elevations
Hepatobiliary: Hepatic function abnormal, hyperbilirubinemia
Skin and subcutaneous tissue: Alopecia, palmar-plantar erythrodysesthesia, rash, skin depigmentation
Renal and urinary: Proteinuria
General: Chest pain
Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)
Nervous system: Ischemic stroke
Cardiac: Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure), myocardial infarction, Torsade de Pointes
Vascular: Cerebral hemorrhage, pulmonary hemorrhage
Gastrointestinal: Gastrointestinal perforation, gastrointestinal fistula
Laboratory Abnormalities: ≥15%
Leukopenia, neutropenia, thrombocytopenia, lymphocytopenia, ALT increased, AST increased, glucose increased, total bilirubin increased, phosphorus decreased, calcium decreased, sodium decreased, potassium increased, creatinine increased, magnesium decreased, glucose decreased.

Summary of adverse reactions in patients with soft tissue sarcoma (STS):
Very common: ≥ 1/10 (≥ 10%)
Metabolism and nutrition: Anorexia, weight decreased
Nervous system: Dizziness, dysgeusia, headache
Cardiac: Bradycardia
Vascular: Hypertension
Respiratory, thoracic and mediastinal: Cough, dyspnea
Gastrointestinal: Abdominal pain, diarrhea, nausea, stomatitis, vomiting
Skin and subcutaneous tissue: Alopecia, exfoliative rash, hair depigmentation, palmar-plantar erythrodysesthesia, skin depigmentation

Musculoskeletal and connective tissue: Musculoskeletal pain, myalgia
General: Chest pain, fatigue, peripheral edema

Common: ≥1/100 and <1/10 (≥ 1% and <10%)
Endocrine: Hypothyroidism
Cardiac: Cardiac dysfunction, myocardial infarction, QT prolongation
Vascular: Epistaxis, gastrointestinal hemorrhage, pulmonary hemorrhage, venous thromboembolic events
Respiratory, thoracic and mediastinal: Dysphonia, pneumothorax
Gastrointestinal: Dyspepsia
Hepatobiliary: Increased ALT and AST
Skin and subcutaneous tissue: Dry skin, nail disorder
General: Chills, blurred vision

Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)
Nervous system: Ischemic stroke
Vascular: Cerebral hemorrhage, hematuria
Gastrointestinal: Gastrointestinal fistula
Hepatobiliary: Hyperbilirubinemia
Skin and subcutaneous tissue: Rash
Renal and urinary: Proteinuria
General: Asthenia

Laboratory Abnormalities: ≥15%:
Leukopenia, neutropenia, thrombocytopenia, lymphocytopenia, anemia, ALKP increased, ALT increased, AST increased, albumin decreased, glucose increased, total bilirubin increased, sodium decreased, potassium increased.

Post Marketing Adverse Drug Reactions

Very common: ≥ 1/10 (≥ 10%)
Musculoskeletal and connective tissue: Arthralgia

Common: ≥1/100 and <1/10 (≥ 1% and <10%)
Infections and infestations (with or without neutropenia
Gastrointestinal: Flatulence
Hepatobiliary: Gamma-glutamyl transpeptidase increased
Musculoskeletal and connective tissue: Muscle spasms

Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)
Blood and lymphatic system: Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome), polycythemia
Eye: Retinal detachment/tear
Gastrointestinal: Pancreatitis

Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)
Nervous system: Posterior reversible encephalopathy syndrome

Respiratory, thoracic and mediastinal: Interstitial lung disease/pneumonitis

15.18 **Drug procurement**: Pazopanib HCl (GW786034) is an investigational agent that will be supplied by Novartis. See Appendix V for detailed drug ordering instructions/form.

15.2 Nursing Guidelines for pazopanib

15.21 Pazopanib should be taken without food (1 hour before or 2 hours after a meal). Should be taken whole with water and not broken or crushed. If a dose is missed, do not take if it is less than 12 hours until the next dose.

15.22 There are numerous drug to drug interactions between pazopanib and other agents metabolized through the P450 system. Assess patient's concomitant medications, including OTC and herbal products. Refer to appendix for medications that should be avoided or used concomitantly with caution.

15.23 Hypertension is the most commonly reported side effect. Monitor blood pressure closely per study guidelines. Administer antihypertensives as ordered by MD.

15.24 Inform patient of possible changes in hair color.

15.25 Gastrointestinal side effects are common (diarrhea, nausea, vomiting, loss of appetite). Treat symptomatically and assess for effectiveness.

15.26 Due to the similarity in nature of this agent to other VEGF inhibitors (bevacizumab, VEGF-trap, etc.) monitor for signs of bleeding, thrombosis and PE. Instruct patient to report any calf tenderness, shortness of breath, chest pain or bleeding immediately.

15.27 Cytopenias are common. Monitor CBC w/diff and instruct patient to report any unusual bruising or bleeding and/or signs of infection to study team.

15.28 Monitor LFT's. Patients who have AST/ALT levels > 3x ULN and concurrent bilirubin >2X ULN should permanently discontinue pazopanib. Patients with AST/ALT levels as above and mild hyperbilirubinemia (with suspected or known Gibert's syndrome) should be monitored weekly while continuing pazopanib.

15.29 Cardiac side effects (CHF, MI, chest pain, etc). while rare can be serious and life threatening. Instruct patient to report any cardiac symptoms to study team immediately.

15.29a RPLS, CVA, and TIA are uncommon, but are life threatening. Instruct patient to report any neurological symptoms to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Overview: This protocol will assess the efficacy of pazopanib in patients with non-clear cell metastatic renal cancer using a one-stage phase II study design.

16.11 Primary Endpoint: The primary endpoint of this trial is the 12-month overall survival rate. A "12-month overall survivor" will be considered synonymous with "success", unless otherwise specified. A patient is considered to be a 12-month survivor if the patient lives 12 months from registration (note, all deaths prior to 12 months, regardless of cause, will be considered a failure). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for the primary endpoint. All eligible patients will be followed until death or a minimum of 2 years.

16.2 Statistical Design:

16.21 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 55%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 75%. The one-stage design based on properties of the binomial distribution uses 39 patients to test the null hypothesis that the true success proportion in a given patient population is at most 55%.

16.22 Sample Size: There will be 35 evaluable patients accrued onto this study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons.

16.23 Accrual Time and Study Duration: The anticipated accrual rate is approximately 1-2 patients per month, based on the incidence of tumor type and the potential to accrue at Mayo Clinic sites (Mayo Clinic Rochester, Mayo Clinic Florida and Mayo Clinic Arizona). Therefore, the accrual period for this phase II study is expected to be 24 months. The final analysis can begin approximately 36 months after the trial begins, i.e. as soon as the last patient has been observed for 12 months.

16.24 Power and Significance Level: The null 12-month overall survival rate of 55% is based on the Kaplan-Meier estimate of 12-month survival from the Mayo Clinic Nephrectomy database (Leibovich, Lohse et al.). Assuming that the number of successes is binomially distributed and the significance level is ≤ 0.10, we are required to accrue evaluable 35 patients to achieve an 80% power under the alternative hypothesis of a 75% success proportion.

16.3 Analysis Plan: The analysis for this trial will commence at the time all patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with standard operating procedures, availability of data for secondary endpoints, and the level of data maturity.

16.31 Primary Endpoint

16.311 The primary endpoint of this trial is the 12-month overall survival rate. This endpoint has been described as a binomial endpoint of success and failure, therefore patients lost to follow-up (eg, progressed/recurred, refusing further study participation, etc) prior to the time necessary for the binomial endpoint (eg, 12 months) will be defined as failure. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable for the primary endpoint. All eligible patients will be followed until death or a minimum of 2 years.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 A tumor response is defined to be a CR or PR noted as the objective status on 2 consecutive evaluations at least 8 weeks apart. Tumor response will be evaluated. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.322 Progression-free survival is defined as the time from registration to the earliest date documentation of disease progression or death. Kaplan-Meier curve will be used to estimate progression-free survival time.

16.323 Adverse events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.324 Observation Phase: Retreatment of patients who have relapsed will be left to the discretion of the treating physician. Statistical analysis of the observational phase data for these patients will be of a descriptive nature.

16.4 Data & Safety Monitoring:

16.41 The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- If 4 or more patients in the first 15 treated patients or anytime thereafter more than 25% of patients experience a ≥grade 4 or higher adverse event, except for hypertension, diarrhea, and abnormal liver function tests, accrual will be temporarily suspended.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The primary and secondary endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 36 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 12 months overall survival status.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by Mayo Clinic sites, has a population which includes approximately 10 % minorities. Based on prior Mayo Clinic sites only studies involving similar disease sites, we expect about 10 % of patients will be classified as minorities by race and about 50 % of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	18	19	37
Ethnic Category: Total of all subjects	19	20	39
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	17	18	35
Racial Category: Total of all subjects	19	20	39

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form[1]	≤2 weeks after registration
Adverse Events: Baseline	
RECIST Measurements: Baseline	
Specimen Submission: Blood (see Section 14.0)	
Specimen Submission: Urine (see Section 14.0)	
Laboratory Tests and Results	
Concomitant Medication Form	
Patient Status: Baseline	
Off Treatment[2]	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. On-Study: Prior Surgery, On-Study Prior Radiation, and On-Study Prior Systemic Therapy will be added as needed.
2. Added if needed based on the responses on the Patient Status: Baseline form

Central Pathology Review Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Pathology Materials (this is for central review, eligibility, etc.)	Submit ≤30 days after registration

Test Schedule Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention)	X[1]	X
Adverse Events: Solicited	X	X
RECIST Measurement[2] s	X	X
Specimen Submission: Blood	X (see Section 14.0)	
Specimen Submission: Urine	X (see Section 14.0)	
Laboratory Tests and Results	X	X
Concomitant Medications	X	X
Patient Status: Treatment	X	
Off Treatment[2]		X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)	
ADR/AER	At each occurrence (see Section 10.0)	

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Added if needed based on the responses on the Patient Status: Treatment form

Follow-up Material(s) -

CRF	Survival Follow-up Phase[1]				
	q. __3__ months until PD	At PD[1]	After PD q. __6__ mos.	Death	New Primary
Patient Status: Survival Follow-up[1]	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for MC1152

18.2 Patient identification labels will be produced for each patient entry. The labels are produced for use on the data forms and will be mailed to the co-sponsors/participants twice. Additional labels may be obtained by directly calling the Mayo Clinic Cancer Center (MCCC) Registration Office [redacted].

18.3 Each co-sponsor/participant will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.4 Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.5 Overdue lists: A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.6 Corrections forms: If a correction is necessary the QAS will query the co-sponsor/participant. The query will be sent to the appropriate co-sponsor/participant who will make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Echocardiogram, screening EKG, CT Head/MRI at baseline, urinalysis cycle 3 and 5, metabolic panel/ CBC Cycle 1 and 2 only, TSH, correlative analysis on blood.

19.3 Other budget concerns:

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APPENDIX 1

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

APPENDIX II

Drugs with Risk of Torsades de Pointes

This list contains medications that are generally accepted (and documented in published data) as having an increased risk of QT prolongation and/or torsades de pointes. **Concomitant administration of pazopanib and a medication on this list is prohibited.**

Generic Name	Brand Name	Comments
Amiodarone	Cordarone®, Pacerone®	Low risk torsades de pointes
Arsenic trioxide	Trisenox®	Torsades de pointes
Bepridil	Vasocor®	
Chloroquine	Aralen®	
Chlorpromazine	Thorazine®	
Cisapride	Propulsid®	Restricted availability in U.S.
Clarithromycin	Biaxin®	
Disopyramide	Norpace®	Torsades de pointes
Dofetilide	Tikosyn®	Torsades de pointes
Dolasetron	Anzemet®	
Droperidol	Inapsine®	Torsades de pointes
Erythromycin	Erythrocin®, E.E.S. ®	IV > PO
Halofantrine	Halfan®	
Haloperidol	Haldol®	IV > PO, high doses increase QT prolongation and torsades de pointes
Ibutilide	Corvert®	Torsades de pointes, female > male, non-Caucasian > Caucasian
Levomethadyl	Orlaam®	
Mesoridazine	Serentil®	
Methadone	Dolophine®, Methadose®	
Pentamidine	Pentam®, Nebupent®	
Pimozide	Orap®	
Procainamide	Pronestyl®, Procan®, Procanbid®	N-acetylprocainamide causes torsade de pointes, not parent compound
Quinidine	Cardioquin®, Quinaglute®	Torsades de pointes
Sotalol	Betapace®	Torsade de pointes female > male
Sparfloxacin	Zagam®	
Thioridazine	Mellaril®	

Note: the above list is not all-inclusive.

References:

Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.

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Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210

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Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.

http://www.azcert.org/medical-pros/druginteractions.cfm Accessed 5/13/11

Drugs with Possible or Conditional Risk of Torsades de Pointes

This list contains medications that, in some reports, have been associated or weakly associated with causing torsades de pointes and/or QT prolongation. There is insufficient data that these medications alone may cause torsades de pointes and/or QT prolongation, however when pazopanib is given concomitantly with a medication on this list (or other risk factors are present such as bradycardia, electrolyte disturbances, congenital long QT syndrome, or concomitant drugs that inhibit metabolism), there may be possible or conditional risk of torsades de pointes and/or QT prolongation. **Extreme caution and careful monitoring should be instituted with concomitant administration of pazopanib and a medication on this list.**

Generic Name	Brand Name	Comments
Alfuzosin	Uroxatral®	
Amantadine	Symmetrel®	Low
Amitriptyline	Elavil®	Nonspecific ECG changes reported.
Atazanavir	Reyataz®	
Azithromycin	Zithromax®	
Chloral hydrate	Noctec®	
Ciprofloxacin	Cipro®	
Citalopram	Celexa®	
Clomipramine	Anafranil®	
Desipramine	Pertofrane®	QT prolongation, VF/sudden death reported
Diphenhydramine	Benadryl®, Nytol®	
Dolasetron	Anzemet®	Granisetron < Ondansetron < Dolasetron
Doxepin	Sinequan®	
Dronedarone	Multaq®	
Escitalopram	Lexapro®, Cipralex®	
Felbamate	Felbatrol®	
Flecainide	Tambocor®	
Foscarnet	Foscavir®	
Fosphenytoin	Cerebyx®	
Fluconazole	Diflucan®	IV > PO
Fluoxetine	Prozac®, Sarafem®	1 in 10,000 ventricular arrhythmias reported
Galantamine	Reminyl®	
Gatifloxacin	Tequin®	
Gemifloxacin	Factive®	
Granisetron	Kytril®	Granisetron < Ondansetron < Dolasetron
Imipramine	Norfranil®	Nonspecific arrhythmias reported
Indapamide	Lozol®	
Isradipine	Dynacirc®	
Itraconazole	Sporanox®	
Ketoconazole	Nizoral®	
Lapatinib	Tykerb®	
Levofloxacin	Levaquin®	Lower risk than that of similar agents
Lithium	Lithobid®, Eskalith®	

Moexipril/HCTZ	Uniretic®	
Moxifloxacin	Avelox®	
Nicardipine	Cardene®	
Nilotinib	Tasigna®	
Nortriptyline	Pamelor®	Nonspecific arrhythmias reported
Octreotide	Sandostatin®	
Ofloxacin	Floxin®	
Ondansetron	Zofran®	Granisetron<Ondansetron< Dolasetron
Oxytocin	Pitocin®	
Paliperidone	Invega®	
Paroxetine	Paxel®	Lower risk than TCA's
Perflutren lipid microspheres	Definity®	
Protriptyline	Vivactil®	
Quetiapine	Seroquel®	QT prolongation
Ranolazine	Ranexa®	
Risperidone	Risperdal®	QT prolongation, sudden death reported
Ritonavir	Norvir®	
Sertraline	Zoloft®	Lower risk than TCA's
Solifenacin	VESIcare®	
Sunitinib	Sutent®	
Tacrolimus	Prograf®	
Tamoxifen	Nolvadex®	
Telithromycin	Ketek®	
Tizanidine	Zanaflex®	
Trazodone	Desyrel®	
Trimethoprim-Sulfa	Sulfa®, Bactrim®, Bactrim DS®	Low
Trimipramine	Surmontil®	
Vardenafil	Levitra®	
Venlafaxine	Effexor®	1 :1000 risk of arrhythmia reported
Voriconazole	VFend®	
Ziprasidone	Geodon®	QT prolongation, 1:1000 risk of arrhythmia

Note: the above list is not all-inclusive.

References:

Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.

Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. *Pharmacotherapy* 2003;23:887-908.

Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210

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Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.

http://www.azcert.org/medical-pros/druginteractions.cfm Accessed 5/13/11

Appendix III
Patient Medication Diary

NAME: _____ I.D. # _____
CYCLE#____

This calendar is for you to indicate that you took the study drugs according to the instructions. Please put a check mark or your initials after each dose and record how many tablets you took.

Please bring the calendar back to your next clinic visit.

	Pazopanib Pill Diary	
Day	**Dose**	**Number of tablets**
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.		
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26.		
27.		
28.		

Signature:_____
Date:_____

Appendix IV

The Stages of Heart Failure – NYHA Classification

In order to determine the best course of of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient 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.

Appendix V

Appendix VI

Inhibitors of CYP3A4

Strong Inhibitors of CYP3A4 > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance
Indinavir (Crixivan®)
Nelfinavir (Viracept®)
Ritonavir (Norvir®)
Clarithromycin (Biaxin®, Biaxin XL®)
Itraconazole (Sporanox®)
Ketoconazole (Nizoral®)
Nefazodone (Serzone®)
Saquinivir (Fortovase®, Invirase®)
Telithromycin (Ketek®)
Moderate Inhibitors of CYP3A4 > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance
Aprepitant (Emend®)
Erythromycin (Erythrocin®, E.E.S. ®, Ery-Tab®, Eryc®, EryPed®, PCE®
Fluconazole (Diflucan®)
Grapefruit juice
Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®)
Diltiazem (Cardizem®, Cardizem CD®, Cardizem LA®, Cardizem SR®, Cartia XT™, Dilacor XR®, Diltia XT®, Taztia XT™, Tiazac®)

Inducers of CYP3A4

Inducers of CYP3A4
Efavirenz (Sustiva®)
Nevirapine (Viramune®)
Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®)
Modafinil (Provigil®)
Phenobarbital (Luminal®)
Phenytoin (Dilantin®, Phenytek®)
Pioglitazone (Actos®)
Rifabutin (Mycobutin®)
Rifampin (Rifadin®)
St. John's wort

Appendix VII

Table 14 Adverse Events Reported for at Least 10% of Subjects (Safety Population) in Study VEG105192

Preferred Term	Number (% of subjects)					
	Placebo (n=145)			Pazopanib (n=290)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AEa	107 (74)	21 (14)	8 (6)	268 (92)	96 (33)	20 (7)
Diarrhea	13 (9)	1 (<1)	0	150 (52)	9 (3)	2 (<1)
Hypertension	15 (10)	1 (<1)	0	115 (40)	13 (4)	0
Hair color changes	4 (3)	0	0	109 (38)	1 (<1)	0
Nausea	13 (9)	0	0	74 (26)	2 (<1)	0
Anorexia	14 (10)	1 (<1)	0	65 (22)	6 (2)	0
Vomiting	11 (8)	3 (2)	0	61 (21)	6 (2)	1 (<1)
Fatigue	11 (8)	2 (1)	2 (1)	55 (19)	7 (2)	0
ALT increased	5 (3)	1 (<1)	0	53 (18)	18 (6)	3 (1)
AST increase	5 (3)	0	0	43 (15)	13 (4)	1 (<1)
Asthenia	12 (8)b	0	0	41 (14)	8 (3)	0
Abdominal pain	2 (1)	0	0	32 (11)	6 (2)	0
Headache	7 (5)	0	0	30 (10)	0	0

a. AEs are ranked by incidence in the pazopanib arm. Any AE, any grade includes Grade 5 (fatal) events (12 [4%]
subjects in the pazopanib arm and 4 [3%] subjects in the placebo arm).
b. One placebo subject had Grade 5 asthenia.
ALT= alanine aminotransferase; AST= aspartate aminotransferase

Appendix VIII

Table 78 Adverse reactions by Organ Class and Frequency, Reported in RCC (VEG105192) and STS (VEG110727) Studies

	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Common	Common
Metabolic and nutrition disorders		
Anorexia	Very common	Very common
Weight decreased	Common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦

	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Cardiac disorders		
Bradycardia^	Very common	Very common
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia	Common	♦
QT prolongation*	Common	Common
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Cerebral haemorrhage*	Uncommon	Uncommon
Epistaxis	Common	Common
Gastrointestinal haemorrhage*	Uncommon	Uncommon
Haematuria	Common	Uncommon
Hypertension*	Very common	Very common
Pulmonary haemorrhage*	Uncommon	Common
Venous thromboembolic events*	Uncommon	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Lipase elevations	Common	♦
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Alanine aminotransferase increased	Very common	Common
Aspartate aminotransferase increased	Very common	Common

	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Hepatic function abnormal	Common	♦
Hyperbilirubinaemia	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair depigmentation	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Very common
Myalgia	♦	Very common
Renal and urinary disorders		
Proteinuria*	Common	Uncommon
General disorders and administration site disorders		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	♦	Common
Fatigue	Very common	Very common
Oedema peripheral	♦	Very common
Vision blurred	♦	Common

* See Warnings and Precautions for additional information.
♦ - Adverse event was not considered causally related to pazopanib in the pivotal clinical trial for this indication.
Note: Laboratory findings, which met the CTC-AE criteria, were recorded as adverse events at the discretion of the Investigator
^ Bradycardia based on heart rate data (heart rates <60 beats per minute)

Table 79 presents laboratory abnormalities occurring in ≥15% of patients who received pazopanib in randomized, placebo-controlled study in RCC. Grades are based on the NCI CTCAE.

Table 79 Selected Laboratory Abnormalities in Greater Than or Equal to 15% of Patients Who Received Pazopanib and More Commonly Than Placebo Arm

	Pazopanib (N = 290)			Placebo (N = 145)		
Parameters	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total Bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Calcium decreased	33	1	1	26	1	<1
Sodium decreased	31	4	1	24	4	1
Potassium increased	27	4	<1	23	5	0
Creatinine increased	26	0	<1	25	<1	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

Table 80 presents laboratory abnormalities occurring in ≥ 15 % of patients who received pazopanib in the pivotal STS study. Grades are based on the NCI CTCAE

Table 80 **Selected Laboratory Abnormalities in Greater than or equal to15% of Subjects Who Received Pazopanib and More Common Than Placebo Arm (VEG110727)**

Parameters	Pazopanib (N = 240)			Placebo (N = 123)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematological						
Leukopenia	44	1	0	15	0	0
Neutropenia	33	4	0	7	0	0
Thrombocytopenia	36	3	<1	6	0	0
Lymphocytopenia	43	10	0	36	9	2
Anaemia	27	5	2	23	<1	<1
Chemistry						
ALKP increased	32	3	0	23	<1	0
ALT increased	46	8	2	18	2	<1
AST increased	51	5	3	22	2	0
Albumin increased	34	<1	0	21	0	0
Glucose increased	45	<1	0	35	2	0
Total Bilirubin increased	29	1	0	7	2	0
Sodium decreased	31	4	0	20	3	0
Potassium increased	16	1	0	11	0	0

Appendix IX

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk

Fax Number: [redacted]

(If you experience difficulty faxing this form, please contact Sheila Bell at 862-778-6763

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

This document contains important safety information.
If fax is received in error, please forward to [redacted]

Version 3.0 Dec 2013

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk

Fax Number: [redacted]

(If you experience difficulty faxing this form, please contact Sheila Bell at 862-778-6763.

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

This document contains important safety information.
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