A Randomized Phase 2 Trial of Pazopanib versus Temsirolimus in Poor-Risk Clear-cell Renal Cell Carcinoma

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1.0 OBJECTIVES

Primary:

- To determine the progression-free survival (PFS) with pazopanib and temsirolimus in patients with advanced poor-risk clear-cell renal cell carcinoma (RCC).

Secondary:

- To determine the objective response rate (CR+PR) in patients with advanced poor-risk clear-cell RCC treated with pazopanib and temsirolimus.
- To determine the overall survival (OS) in patients with advanced poor-risk clear-cell RCC treated with pazopanib and temsirolimus.
- To determine the time to progression (TTP) in patients with advanced poor-risk clear-cell RCC treated with pazopanib and temsirolimus.
- To determine the duration of response in patients with advanced poor-risk clear-cell RCC treated with pazopanib and temsirolimus.
- To determine the safety associated with pazopanib and temsirolimus in patients with advanced poor-risk clear cell RCC.

Tertiary:

- To perform informative correlative studies in this disease state.
- To determine the safety and patient reported outcomes.

2.0 BACKGROUND AND RATIONALE

2.1 Renal Cell Carcinoma (RCC)

Renal cell carcinoma comprises more than 90% of kidney cancer cases and accounts for approximately 2-4 % of all adult malignancies. In 2008, approximately 54,000 people in the United States were diagnosed with kidney cancer (renal cell cancer and transitional cell carcinoma of the renal pelvis) and approximately 13,000 died secondary to metastatic disease. Approximately 25 % of patients with RCC present with metastasis at the time of initial diagnosis and up to 20-30 % of patients develop recurrent disease after nephrectomy. Surgical removal of the primary tumor is the only effective therapy in the non-metastatic setting. No adjuvant therapy has been shown yet to alter the clinical course even in patients at high-risk for developing metastatic disease.

Metastatic RCC (mRCC) is a heterogeneous disease with variable clinical outcome. Two randomized phase III trials have provided support for performing cytoreductive nephrectomy in mRCC, although the most optimal timing of this procedure has not been determined. Some patients with solitary metastasis, who are candidates for complete metastasectomies, can

achieve a long-term survival; however, once metastases develop in multiple organs, systemic therapies, until recently, have had little effect on the clinical course for the majority of patients. Immunotherapy with interleukin-2, interferon-alfa, or a combination of these two cytokines, has been the main therapy in mRCC for two decades, but benefits only a small percentage of patients. In an effort to objectively compare different therapies in the same trial and similar therapies across trials, prognostic models have been developed to assign patients to different risk categories based on pretreatment clinical features. Cytokines (interleukin-2, interferon alfa) have recently been replaced by agents targeting the VEGF or the m-TOR pathways.

2.2 Targeted Therapies in MRCC

Advances in the understanding of the genetic mutation or silencing of the tumor suppressor gene, known as the von Hippel-Lindau (VHL) gene, have shown that this abnormal gene produces a deviant protein which causes the accumulation of hypoxia inducible factors (HIF), which in turn induce the production of products which are critical to the proliferation of clear-cell RCC. Three of these products are vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and transforming growth factor-alpha (TGF-α). All four of these cellular products, i.e., HIF, VEGF, PDGF and TGF-α, have constituted rational targets of novel therapies.

Pazopanib is a multi-tyrosine kinase inhibitor that selectively inhibits protein tyrosine kinase receptors including VEGFR1-3, PDGFRα/β, c-Kit, and Flt-3. Pazopanib demonstrated substantial anti-tumor activity in a phase II trial in mRCC with randomized discontinuation design (Hutson et al, 2009). A randomized phase III trial comparing pazopanib to placebo, either as first-line therapy in treatment-naïve patients, or after failure of one cytokine in 435 patients with advanced clear-cell RCC showed significant prolongation of median PFS in favor of pazopanib (9.2 months vs. 4.2 months for all patients, $p<0.0000001$;11.1 months vs.2.8 months for treatment-naïve patients, $p<0.0000001$;7.4 months vs. 4.2 months for cytokine-pretreated patients).

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in vitro studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor. The clinical benefit of temsirolimus for poor-risk, advanced RCC patients was demonstrated in a Phase III study comparing temsirolimus, with interferon alpha (IFN-alpha), or combined temsirolimus plus IFN-alpha as first-line treatment of advanced RCC. It showed that treatment with temsirolimus alone significantly increased median overall survival in poor-risk, advanced RCC patients (10.9 vs 7.3 vs

8.4 months). This was the first Phase III trial to demonstrate an overall improvement in survival using an agent as "targeted therapy" for patients with advanced RCC.

The targeted agents discussed above, although not curative, represent a significant progress in the management of mRCC.

2.3 Rationale

In the past few years, considerable progress has been made in the management of patients with metastatic renal cell carcinoma (RCC). There are now six (five in the first-line setting) FDA-approved treatments for metastatic RCC, however most patients experience disease progression within a year or less. The vast majority of metastatic RCC patients who were enrolled on phase 3 trials with anti-VEGF therapies, sorafenib, sunitinib, pazopanib and bevacizumab plus interferon alfa had good- or intermediate-risk disease. Temsirolimus is the standard of care for the treatment of patients with advanced poor-risk RCC, based on results from a phase 3 trial comparing single-agent temsirolimus versus single-agent interferon alfa versus the combination of temsirolimus and interferon alfa. The response rate of temsirolimus in this study was 8.4 %, and the median PFS and median OS were 3.8 months and 10.9 months, respectively. There is no data on the efficacy of multityrosine kinase inhibitors (TKI) in this disease state. Therefore, it is important to investigate agents with the oral convenience and tolerability of TKIs, such as pazopanib, in advanced poor-risk RCC.

3.0 BACKGROUND DRUG INFORMATION

3.1 Pazopanib

3.1.1 Description

Pazopanib is a tyrosine kinase inhibitor (TKI). Pazopanib is presented as the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. It has the molecular formula C21H23N7O2S•HCl and a molecular weight of 473.99.

Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

Tablets of pazopanib are for oral administration and is supplied in a 200 mg film-coated tablet. Each film-coated tablet contains pazopanib hydrochloride equivalent to 200 mg of pazopanib free base. The inactive ingredients of pazopanib are: Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. Coating: Hypromellose, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, titanium dioxide and may contain iron oxide black , yellow, or red depending on tablet

color. The 200 mg tablets of pazopanib are modified capsule-shaped, gray, film-coated with GS JT debossed on one side. Pazopanib should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Pazopanib is being provided by the study supporter, Novartis.

3.1.2 Preclinical Studies

Pazopanib is a potent, multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR-1, -2, -3, PDGFR-α and -β and c-kit, with half-maximal inhibition (IC50) values of 10, 30, 47, 71, 84 and 74nM, respectively. It inhibits VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells (HUVEC) as well as in mouse lungs in a dose-dependent manner. Data from preclinical studies show pazopanib has significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibits basic fibroblast growth factor- (bFGF-) and VEGF-induced angiogenesis in two mouse models of angiogenesis, viz., the Matrigel plug assay and the cornea micropocket model.

3.1.3 Clinical Studies

Glaxo SmithKline (GSK) initiated the clinical development of pazopanib in December 2002. As of September 2008, a total of 38 clinical studies (including some initiated by the United States National Cancer Institute) have been conducted or are in progress in adult subjects with cancer, including renal cell carcinoma, ovarian cancer, breast cancer, soft tissue sarcoma, cervical cancer, non-small cell lung cancer, multiple myeloma, glioma, colorectal cancer, and hepatocellular cancer.

As of September 2008, approximately 1600 cancer subjects have received pazopanib in clinical studies. The most common adverse events (AEs) reported to date include diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminontransferase (AST) and alanine aminontransferase (ALT) increases, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (NCI-CTCAE). The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon. The most common serious adverse events (SAEs) occurring in subjects enrolled in pazopanib studies as of September 2008, regardless of treatment assignment include diarrhea, abdominal pain, vomiting, dyspnea, hypertension (including one SAE of hypertensive crisis), pyrexia, anemia, dehydration, fatigue, pneumonia, pleural effusion, neutropenia, pulmonary embolism, ALT increased, and nausea.

3.1.4 Pharmacokinetics

Absorption: Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean AUC and Cmax of 1,037 hr microg/mL and 58.1 microg/mL (equivalent to 132 microM), respectively. There was no consistent increase in AUC or Cmax at pazopanib doses above 800 mg.

Administration of a single pazopanib 400 mg crushed tablet increased AUC(0-72) by 46% and Cmax by approximately 2 fold and decreased tmax by approximately 2 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets of pazopanib should not be crushed.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and Cmax. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

Distribution: Binding of pazopanib to human plasma protein in vivo was greater than 99% with no concentration dependence over the range of 10 to 100 mg/mL. In vitro studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

Metabolism: In vitro studies demonstrated that pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

Elimination: Pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose.

Hepatic Impairment: Interim data from a dose escalation study assessed the influence of hepatic impairment on the safety and pharmacokinetics of pazopanib in cancer patients with normal hepatic function and in patients with mild, moderate, and severe hepatic impairment. The starting doses were 800, 400, 200, and 100 mg once daily for patients with normal hepatic function and patients with mild, moderate, and severe hepatic impairment, respectively.

Pharmacokinetic data from patients with normal hepatic function (n = 12) and moderate (n = 7) hepatic impairment indicate that pazopanib clearance was decreased by 50% in those with moderate hepatic impairment. The maximum tolerated pazopanib dose in

patients with moderate hepatic impairment is 200 mg once daily. There are no data on patients with mild or severe hepatic impairment.

Drug Interactions: Coadministration of oral pazopanib with CYP3A4 inhibitors has resulted in increased plasma pazopanib concentrations. Concurrent administration of a single dose of pazopanib eye drops with the strong CYP3A4 inhibitor and Pgp inhibitor, ketoconazole, in healthy volunteers resulted in 220% and 150% increase in mean AUC(0-t) and Cmax values, respectively.

Administration of 1,500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp, and BCRP, with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean pazopanib AUC(0-24) and Cmax compared to administration of 800 mg pazopanib alone.

In vitro studies with human liver microsomes showed that pazopanib inhibited the activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and Cmax of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Coadministration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and Cmax, respectively.

In vitro studies also showed that pazopanib inhibits UGT1A1 and OATP1B1 with IC50s of 1.2 and 0.79 microM, respectively. Pazopanib may increase concentrations of drugs eliminated by UGT1A1 and OATP1B1.

CYP3A4 Inhibitors: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for pazopanib should be considered when it must be coadministered with strong CYP3A4 inhibitors [see Section 6.1.1.3]. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

CYP3A4 Inducers: 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.

A comprehensive list of cytochrome p450 3A4 inducers and inhibitors may be found at: http://www.medicine.iupui.edu/clinpharm/ddis/table.asp

3.1.5 Pazopanib Drug Interactions

Clinically relevant drug interactions: substrates, inducers, and inhibitors of isoenzyme CYP3A

<table>
<tr><td colspan="2">SUBSTRATES</td></tr>
<tr><td>Antibiotics:
Clarithromycin, erythromycin, telithromycin</td><td>Calcium channel blockers:
Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil</td></tr>
<tr><td>Anti-arrhythmics:
Quinidine</td><td>HMG CoA reductase inhibitors:
Cerivastatin, lovastatin, simvastatin</td></tr>
<tr><td>Benzodiazepines:
Alprazolam, diazepam, midazolam, triazolam</td><td>Steroid 6beta-OH:
estradiol, hydrocortisone, progesterone, testosterone</td></tr>
<tr><td>Immune modulators:
Cyclosporine, tacrolimus (FK506)</td><td rowspan="4">Miscellaneous:
Alfentanil, aprepitant, aripirazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine-N-demethylation, dapsone, dexamethasone, dextromethorphan, docetaxel domperidone, eplerenone, fentanyl, finasteride, Gleevec/imatinib, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, risperidone, salmeterol, sildenafil, sirolimus, sorafenib, sunitinib, tamoxifen, taxol, terfenadine, temsirolimus, trazodone, vincristine, zaleplon, ziprasidone, zolpidem</td></tr>
<tr><td>HIV Antivirals:
Indinavir, nelfinavir, ritonavir, saquinavir</td></tr>
<tr><td>Prokinetic:
Cisapride</td></tr>
<tr><td>Antihistamines:
Astemizole, chlorpheniramine, terfenadine</td></tr>
<tr><td colspan="2">INDUCERS</td></tr>
<tr><td colspan="2">Barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John’s wort, troglitazone, efavirenz, nevirapine</td></tr>
<tr><td colspan="2">INHIBITORS</td></tr>
<tr><td colspan="2">Strong inhibitors:
indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin,
Posaconazole (Krishna et al, 2009)
Moderate inhibitors:
aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil

Weak inhibitors:
Cimetidine,
Seville orange (Malhotra et al, 2001)</td></tr>
</table>

Unclassified as per the Indiana University DDI listing: Ciprofloxacin, delaviridine, troleandamycin, mibefradil, amiodarone, chloramphenicol, diethyldithiocarbamate, fluvoxamine, starfruit, gestodene, imatinib, mifepristone, norfloxacin, norfluoxetine, voriconazole

Based on http://medicine.iupui.edu/clinpharm/ddis/table.asp as of December 01, 2009 *
Voriconazole (unclassified as per the Indiana University DDI table)
Strong inhibitor according to the following reference:
(http://www.nature.com/clpt/journal/v80/n5/pdf/clpt2006438a.pdf)

Clinically relevant drug interactions mediated by PgP

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole, ketocoanzole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	rifampin, St John's wort

Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Dec. 2, 2009, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table."

NOTES:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf

3.1.6 Clinical Safety:

a. Hepatic Toxicity:

In a controlled clinical study with pazopanib for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the pazopanib and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received pazopanib and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on pazopanib and 2/145 (1%) on placebo. [See Dosage and Administration (2.2) and Warnings and Precautions (5.1).]

b. QT Interval Prolongation and Torsade de Pointes

Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using pazopanib, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase pazopanib plasma concentrations, should be used with caution and dose reduction of pazopanib should be considered.

c. Hypertension

Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of pazopanib is recommended until hypertension is controlled.

d. Hemorrhagic events

Tumor-related hemorrhage has been observed in patients treated with pazopanib. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred rarely in patients with intra-abdominal malignancies treated with pazopanib.

e. Hypothyroidism

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of hypothyroidism on pazopanib treatment. Patients with signs or symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

f. QT Prolonging Medications

Certain medications that are associated with a risk for QTc prolongation, although not prohibited, should be avoided or replaced with medications that do not carry these risks, if possible.

QT_c prolongation is a rare but serious adverse event associated with pazopanib. Caution should be exercised when administering pazopanib to subjects with a history of QT_c interval prolongation, in subjects taking anti-arrhythmics or

other medications that may prolong the QT_c interval, and those with relevant pre-existing cardiac disease (i.e. amiodarone, clarithromycin, disopyramide, haloperidol, methadone, procainamide; some SSRIs such as citalopram, fluoxetine, venlafexine; and fluoroquinolones such as ciprofloxacin, levofloxacin, and moxifloxacin). See Appendix F for a more comprehensive list of drugs that may prolong Qt interval.

*Note these medication lists are not all inclusive and are as only a reference of potential drug-drug interactions. A useful website for a more inclusive list may be found at: http://www.azcert.org/index.cfm

See PAZOPANIB package insert for additional drug information.

3.2 Temsirolimus

3.2.1 Description

Temsirolimus is a white to off-white powder with a molecular formula of C56H87NO16 and a molecular weight of 1030.30. It is non-hygroscopic. Temsirolimus is practically insoluble in water and soluble in alcohol. It has no ionizable functional groups, and its solubility is independent of pH.

The chemical name of temsirolimus is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14, 21,22,23,24, 25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone 4′- [2,2-bis(hydroxymethyl) propionate]; or Rapamycin, 42-[3-hydroxy-2-(hydroxymethyl)- 2-methylpropanoate].

Temsirolimus injection, 25 mg/mL, is a clear, colorless to light yellow, nonaqueous, ethanolic, sterile solution. Temsirolimus injection requires two dilutions prior to intravenous infusion. Temsirolimus injection should be diluted only with the supplied diluent.

Supplied diluent is a sterile, non-aqueous solution that is supplied with temsirolimus injection, as a kit. Active ingredient: temsirolimus (25 mg/mL). Inactive ingredients: dehydrated alcohol (39.5% w/v), dl-alpha-tocopherol (0.075% w/v), propylene glycol (50.3% w/v), and anhydrous citric acid (0.0025% w/v). Diluent inactive ingredients: polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v) and dehydrated alcohol (19.9% w/v).

After the temsirolimus injection vial has been diluted with supplied diluent, in accordance with the instructions below, the solution contains 35.2% alcohol.

Temsirolimus injection and supplied diluent are filled in clear glass vials with butyl rubber stoppers. Each kit is supplied in a single carton containing one single-use vial of 25 mg/mL of temsirolimus and one diluent vial which includes a deliverable volume of 1.8 mL, and must be stored at 2°-8°C (36° 46°F). Protect from light.

3.2.1.1 Preparation and Administration

Temsirolimus must be stored under refrigeration at 2°-8°C (36°-46°F) and protected from light. During handling and preparation of admixtures, temsirolimus should be protected from excessive room light and sunlight. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

In order to minimize the patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final temsirolimus dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Dilution: In preparing the temsirolimus administration solution, follow this two-step dilution process in an aseptic manner.

Step 1: Inject 1.8 mL of supplied diluent into the vial of temsirolimus injection(25 mg/ml). The temsirolimus vial contains an overfill of 0.2 mL (30 mg/1.2 mL).

Due to the intentional overfill in the temsirolimus injection vial, the drug concentration of the resulting solution will be 10 mg/mL. A total volume of 3 mL will be obtained including the overfill. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates. The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature.

Step 2: Withdraw the required amount of temsirolimus from the 10 mg/mL drug solution/diluents mixture prepared in Step 1. Inject rapidly into a 250 mL container (glass, polyolefin, or polyethylene) of 0.9% sodium chloride injection.

Mix the admixture by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.

Administration: The sodium chloride injection container should be composed of non-DEHP containing materials, such as glass, polyolefin or polyethylene, and the administration set should consist of non-DEHP tubing to avoid extraction of di-(2-ethylhexyl) phthalate (DEHP).

Temsirolimus contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from PVC. An in line polyethersulfone filter with a pore size of not greater than 5 microns is recommended for administration.

The final diluted solution of temsirolimus is intravenously infused over a 30-60 minute period once a week. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the drug.

Administration of the final diluted infusion solution should be completed within six hours from the time that the drug solution/diluent mixture is added to the sodium chloride injection.

3.2.1.2 Compatibilities and Incompatibilities

Undiluted temsirolimus injection should not be added directly to aqueous infusion solutions. Direct addition of temsirolimus injection to aqueous solutions will result in precipitation of drug. Always combine temsirolimus injection with supplied diluent before adding to infusion solutions. It is recommended that temsirolimus be administered in 0.9% sodium chloride injection after combining with supplied diluent. The stability of temsirolimus in other infusion solutions has not been evaluated. Addition of other drugs or nutritional agents to admixtures of temsirolimus in sodium chloride injection has not been evaluated and should be avoided. Temsirolimus is degraded by both acids and bases, and thus combinations of temsirolimus with agents capable of modifying solution pH should be avoided.

3.2.2 Preclinical Studies

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in vitro studies using renal cell carcinoma cell

lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor. In other preclinical models, it appeared that the agent decreased proliferation of murine xenografts bearing various solid tumors, including glioma, breast and prostate cancer.

3.2.3 Clinical Studies

A phase 3, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving temsirolimus and temsirolimus plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, more than one metastatic organ site). Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n=207), temsirolimus alone (25 mg weekly; n=209), or the combination arm (n=210).

The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy.

The median duration of treatment in the temsirolimus arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks).

There was a statistically significant improvement in OS (time from randomization to death) in the temsirolimus 25 mg arm compared to IFN-α. The combination of temsirolimus 15 mg and IFN-α did not result in a significant increase in overall survival when compared with IFN-α alone.

3.2.4 Pharmacokinetics

Absorption: Following administration of a single 25 mg dose of temsirolimus in patients with cancer, mean temsirolimus Cmax in whole blood was 585 ng/mL (coefficient of variation, CV =14%), and mean AUC in blood was 1627 ng•h/mL (CV=26%). Typically Cmax occurred at the end of infusion. Over the dose range of 1 mg to 25 mg, temsirolimus exposure increased in a less than dose proportional manner while

sirolimus exposure increased proportionally with dose. Following a single 25 mg intravenous dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus.

Distribution: Following a single 25 mg intravenous dose, mean steady-state volume of distribution of temsirolimus in whole blood of patients with cancer was 172 liters. Both temsirolimus and sirolimus are extensively partitioned into formed blood elements.

Metabolism: Cytochrome P450 3A4 is the major isozyme responsible for the formation of five temsirolimus metabolites. Sirolimus, an active metabolite of temsirolimus, is the principal metabolite in humans following intravenous treatment. The remainder of the metabolites account for less than 10% of radioactivity in the plasma. In human liver microsomes temsirolimus was an inhibitor of CYP2D6 and 3A4. However, there was no effect observed in vivo when temsirolimus was administered with desipramine (a CYP2D6 substrate), and no effect is anticipated with substrates of CYP3A4 metabolism.

Elimination: Elimination is primarily via the feces. After a single IV dose of [14C]-temsirolimus approximately 82% of total radioactivity was eliminated within 14 days, with 4.6% and 78% of the administered radioactivity recovered in the urine and feces, respectively. Following a single25 mg dose of temsirolimus in patients with cancer, temsirolimus mean (CV) systemic clearance was 16.2 (22%) L/h. Temsirolimus exhibits a bi-exponential decline in whole blood concentrations and the mean half-lives of temsirolimus and sirolimus were 17.3 hr and 54.6 hr, respectively.

Drug Interactions: Co-administration of temsirolimus with rifampin, a potent CYP3A4/5 inducer, had no significant effect on temsirolimus Cmax (maximum concentration) and AUC (area under the concentration versus the time curve) after intravenous administration, but decreased sirolimus Cmax by 65% and AUC by 56% compared to temsirolimus treatment alone. If alternative treatment cannot be administered, a dose adjustment should be considered. Co-administration of temsirolimus with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus Cmax or AUC; however, sirolimus AUC increased 3.1-fold, and Cmax increased 2.2-fold compared to temsirolimus alone. If alternative treatment cannot be administered, a dose adjustment should be considered. The concentration of desipramine, a CYP2D6 substrate, was unaffected when 25 mg of temsirolimus was co-administered. No clinically significant effect is anticipated when temsirolimus is co-administered with agents that are metabolized by CYP2D6 or CYP3A4.

3.2.4.1 Temsirolimus Drug Interactions

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g. ketoconazole, itraconazole, clarithromycin,

atazanavir, indinavir,nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a temsirolimus dose reduction to 12.5 mg/week should be considered. This dose of temsirolimus is predicted to adjust the AUC to the range observed without inhibitors.

However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the temsirolimus dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor. (see previous table in 6.1.1.3)

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a temsirolimus dose increase from 25 mg/week up to 50 mg/week should be considered. This dose of temsirolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the temsirolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer

3.2.5 Clinical Safety

Hypersensitivity Reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, and chest pain have been observed with temsirolimus Temsirolimus should be used with caution in persons with known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any other component (including the excipients) of temsirolimus.

An H1 antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion. Temsirolimus should be used with caution in patients with known hypersensitivity to an antihistamine, or patients who cannot receive an antihistamine for other medical reasons.

If a patient develops a hypersensitivity reaction during the temsirolimus infusion, the infusion should be stopped and the patient should be observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed with the administration of an H1-receptor antagonist (such

as diphenhydramine), if not previously administered, and/or an H2-receptor antagonist (such as intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the temsirolimus infusion. The infusion may then be resumed at a slower rate (up to 60 minutes).

Hepatic Impairment

The safety and pharmacokinetics of temsirolimus were evaluated in a dose escalation phase 1study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin >1.5 x ULN experienced greater toxicity than patients with baseline bilirubin ≤1.5 x ULN when treated with temsirolimus. The overall frequency of ≥ grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin >1.5 x ULN. temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN due to increased risk of death. Use caution when treating patients with mild hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. If temsirolimus must be given in patients with mild hepatic impairment (bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin ≤ULN), reduce the dose of temsirolimus to15 mg/week.

Hyperglycemia/Glucose Intolerance

The use of temsirolimus is likely to result in increases in serum glucose. In the phase 3 trial, 89% of patients receiving temsirolimus had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy. Serum glucose should be tested before and during treatment with temsirolimus. Patients should be advised to report excessive thirst or any increase in the volume or frequency of urination.

Infections

The use of temsirolimus may result in immunosuppression. Patients should be carefully observed for the occurrence of infections, including opportunistic infections

Interstitial Lung Disease

Cases of interstitial lung disease, some resulting in death, occurred in patients who received temsirolimus. Some patients were asymptomatic with infiltrates detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, hypoxia, and fever. Some patients required discontinuation of temsirolimus and/or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Hyperlipemia
The use of temsirolimus is likely to result in increases in serum triglycerides and cholesterol. In the phase 3 trial, 87% of patients receiving temsirolimus had at least one elevated serum cholesterol value and 83% had at least one elevated serum triglyceride value. This may require initiation, or increase in the dose, of lipid-lowering agents. Serum cholesterol and triglycerides should be tested before and during treatment with temsirolimus.

Bowel Perforation
Cases of fatal bowel perforation occurred in patients who received temsirolimus. These patients presented with fever, abdominal pain, metabolic acidosis, bloody stools, diarrhea, and/or acute abdomen. Patients should be advised to report promptly any new or worsening abdominal pain or blood in their stools.

Renal Failure
Cases of rapidly progressive and sometimes fatal acute renal failure not clearly related to disease progression occurred in patients who received temsirolimus. Some of these cases were not responsive to dialysis.

Wound Healing Complications
Use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perioperative period.

Intracerebral Hemorrhage
Patients with central nervous system tumors (primary CNS tumor or metastases) and/or receiving anticoagulation therapy may be at an increased risk of developing intracerebral bleeding (including fatal outcomes) while receiving temsirolimus.

Co-administration with Inducers or Inhibitors of CYP3A Metabolism
Agents Inducing CYP3A Metabolism:
Strong inducers of CYP3A4/5 such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, rifabutin, and rifampacin may decrease exposure of the active metabolite, sirolimus. If alternative treatment cannot be administered, a dose adjustment should be considered. St. John's Wort may decrease temsirolimus plasma concentrations unpredictably. Patients receiving temsirolimus should not take St. John's Wort concomitantly.

Agents Inhibiting CYP3A Metabolism:
Strong CYP3A4 inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may

increase blood concentrations of the active metabolite sirolimus. If alternative treatments cannot be administered, a dose adjustment should be considered.

Vaccinations
The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with temsirolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

Pregnancy
Pregnancy Category D: Temsirolimus administered daily as an oral formulation caused embryo-fetal and intrauterine toxicities in rats and rabbits at human sub-therapeutic exposures. Embryo-fetal adverse effects in rats consisted of reduced fetal weight and reduced ossifications, and in rabbits included reduced fetal weight, omphalocele, bifurcated sternabrae, notched ribs, and incomplete ossifications .In rats, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of 2.7 mg/m^2/day (approximately 0.04-fold the AUC in cancer patients at the human recommended dose). In rabbits, the intrauterine and embryo-fetal adverse effects were observed at the oral dose of ≥7.2 mg/m^2/day (approximately 0.12-fold the AUC in cancer patients at the recommended human dose).
Women of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for 3 months after temsirolimus therapy has stopped. Temsirolimus can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Men should be counseled regarding the effects of temsirolimus on the fetus and sperm prior to starting treatment. Men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of temsirolimus.

4.0 ELIGIBILITY CRITERIA

4.1 INCLUSION

1. Pathologic confirmation of metastatic or locally advanced RCC with a major clear cell component.
2. Measurable disease by RECIST criteria.
3. Age ≥18 years

4. ECOG performance status 0-2 or Karnofsky Performance Status ≥ 60%

5. Meets criteria for poor-risk defined as 3 or more of the following: ECOG performance status 2, anemia (hemoglobin lower than reference range), elevated serum LDH >1.5x upper limit of normal (ULN), hypercalcemia (corrected serum calcium level > upper limit of normal), time from initial RCC diagnosis to registration on this trial < 1 year, and > 1 metastatic organ sites.

6. Adequate organ and marrow function within 14 days of registration as defined below:

- Absolute neutrophil count ≥1,500/µL
- Platelets ≥100,000/µL
- Hgb ≥ 9.0 g/dL (transfusion allowed)
- Renal: serum creatinine ≤ 1.5 x ULN or calculated CrCl ≥40 cc/min and random urine protein:creatitine ratio (UPC) < 1 or 24-hr urine protein < 1g
- Liver: total bilirubin ≤ 1.5 mg/dl; AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN for subjects without evidence of liver metastases, ≤ 5 x ULN for subjects with documented liver metastases
- INR ≤ 1.2 x ULN; PTT ≤ 1.5 x ULN. Therapeutic anticoagulation with warfarin is allowed if target INR ≤ 3 on a stable dose of warfarin or on a stable dose of LMW heparin for > 2 weeks (14 days) at time of randomization.

7. Female patients of childbearing potential (not postmenopausal for at least 12 months and not surgically sterile) must have a negative serum or urine pregnancy test within 14 days of study registration. Pregnancy test must be repeated if performed > 14 days before starting study drug.

4.2 EXCLUSION

1. Prior malignancy, except for non-melanoma skin cancer, in situ carcinoma of any site, or other cancers for which the patient has been adequately treated and disease free for 2 years

2. Prior targeted therapy (anti-VEGF agents or mTOR inhibitors) including adjuvant therapy, and prior chemotherapy for mRCC. However, prior immunotherapy (cytokines or vaccines) is allowed.

3. Any experimental drug while on this study; however, concomitant bone targeted therapy (bisphosphonates or the anti-RANK ligand denosumab) is allowed.

4. Uncontrolled brain metastases and infections. Patients with brain metastases treated with Gamma Knife (GK) or with whole brain radiation within 24 hours of registration.

5. History of stroke within 6 months of registration

6. Clinically significant cardiovascular disease, defined as myocardial infarction (or unstable angina) within 6 months of registration, New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac dysrhythmia refractory to medical management However, treated and controlled or stable/not clinically significant cardiovascular disease is allowed per evaluation by cardiologist.

7. Uncontrolled hypertension (home blood pressure readings are permitted) or prior history of hypertensive crisis or hypertensive encephalopathy; however, treatment of hypertension with medications is permitted.

8. History of uncontrolled hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1

9. Significant vascular disease including aortic aneurysm, aortic dissection.

10. Symptomatic peripheral vascular disease

11. Pregnancy

12. HIV-positive patients receiving combination anti-retroviral therapy

13. Coagulopathy or bleeding diathesis

14. Concomitant treatment with rifampin, St. John's wort, or the cytochrome p450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or Phenobarbital)

15. Major surgery within 28 days prior to registration

16. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device within 7 days prior to starting drug

17. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study registration

18. Serious non-healing wound

19. Baseline $QT_cB \geq 470$ msec.

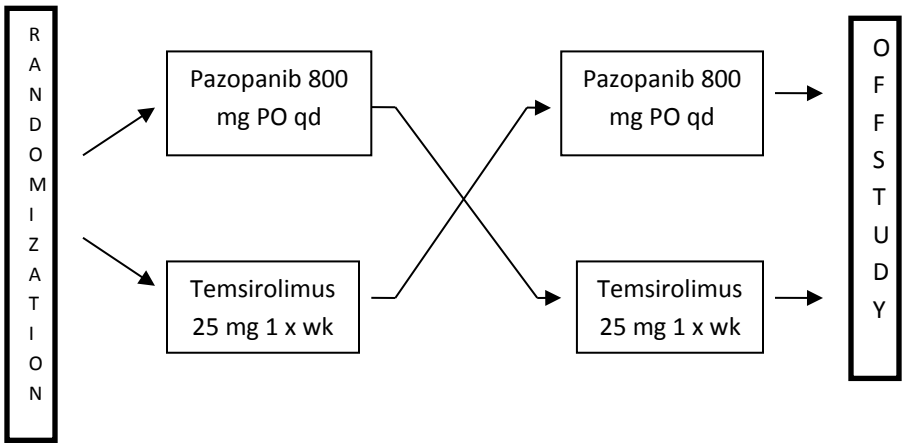
5.0 TREATMENT PLAN

5.1 Study Summary

Patients with advanced poor-risk clear-cell RCC who have not had any prior systemic targeted therapy will be randomized fairly in a 1:1 ratio to receive pazopanib or temsirolimus as first-line therapy. Patients will be stratified upfront by nephrectomy status (yes/no) and prior cytokine/vaccine therapy (yes/no). At the time of disease progression, patients will be offered the option of crossover to receive the agent they did not receive in the first-line.

5.2 Administration

After registration on the protocol, patients will be randomized to receive either pazopanib or temsirolimus treatment. Following randomization patients will begin treatment with the first assigned agent. At progression, if they have not suffered an adverse event that would preclude them from continuing with systemic therapy, after the applicable washout period, will begin treatment with the remaining treatment agent at the discretion of the physician.



Pazopanib will be taken at 800 mg PO daily without food (at least 1 hour before or 2 hours after a meal) until PD or prohibitive toxicity or withdrawal of consent. Tablets will not be crushed due to the potential for increased rate of absorption which may affect systemic exposure. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose. Patients will complete a pill diary for pazopanib to document compliance.

Temsirolimus will be given at 25 mg IV infused over 30-60 minutes every week until PD or prohibitive toxicity or withdrawal of consent. Patients will receive prophylactic intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of temsirolimus.

A cycle consists of 4 weeks of therapy. Pazopanib will be self-administered at home and in the outpatient setting for patients who receive temsirolimus.

All patients will have a washout period of 2 weeks from the day of progressive disease tumor assessment before they start 2nd-line therapy.

5.3 Evaluation before treatment

Within 4 weeks of registration:
* A standing window of allowance equal to +/- 3 days will be utilized.

- All participants must sign a consent form agreeing to participate in the study

- Baseline radiological studies should include CT scans of the chest (high-resolution) and abdomen and MRI of the brain. Additional studies (e.g., CT scan of pelvis, bone scan, plain films) should be obtained as appropriate. MRI of the abdomen and/or CT scan of the brain can be substituted at the physician's discretion.

- Cardiac evaluation with a 12-lead EKG and an echocardiogram or MUGA. The echocardiogram or MUGA scan may be obtained within 12 weeks of registration.

- A minimum of 7 days must elapse between the diagnostic biopsy and treatment if tissue diagnosis was not previously made.

- Optional: Previously collected tissue will be requested from patients who consent, and will be stored for future research related to cancer. Tissue will also be collected during procedures performed while patients are enrolled in this study. No new procedures will be required. This tissue will also be banked as described above.

5.3.1 Within 14 days of registration:

* A standing window of allowance equal to +/- 2 days will be utilized.

- All patients must undergo a complete history and physical examination, including vital signs, ECOG performance status, height, current weight including recent weight loss, Concurrent non-malignant disease and medications must be documented. All prior surgical procedures or radiation treatments must be recorded in detail.

- Laboratory studies should include CBC w/ platelet count and differential, chemistry panel (total protein, albumin, alkaline phosphatase, AST, ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide), fasting lipid panel, free T4, thyroid stimulating hormone (TSH), PT and PTT. Serum amylase and lipase will be done only if clinically indicated. Patients will have a U/A. Patients who have urine protein ≥ 300 on U/A should have a random UPC ratio at baseline. A pregnancy test (serum/plasma or urine betaHCG) in female patients of childbearing potential will also be included.

- All patients will complete a full Quality of Life assessment battery (see Section 7 for additional details)

- Optional baseline blood specimens for future correlative studies will be collected.

5.4 Evaluation During Treatment (initial treatment or crossover)

*Evaluations while on study will have a standing window of allowance equal to +/- 7 days.

Treatment evaluations will consist of the following study activities (a cycle is 4 weeks):

- Interim medical history and physical examination, including vital signs, height, current weight including recent weight loss every 4 weeks for temsirolimus patients. (May be done by local physician every other cycle for temsirolimus patients only). Interim medical history and physical examination, including vital signs, current weight including recent weight loss every 8 weeks for pazopanib patients.

- All patients will complete a follow-up Quality of Life assessment battery (see Section 7 for additional details)

- Weekly blood pressure monitoring for the first four weeks for patients receiving pazopanib, and then with each history and physical every 8 weeks. Monitoring may be performed at doctor's office or by the patient at home using an electronic blood pressure device. Blood pressure measurements performed outside of the office of the treating physician should be recorded by the patient and submitted to the treating physician during cycle one. An increase in blood pressure to > 160 systolic or > 100 diastolic should be reported to the treating physician immediately.

- Urinalysis (U/A) every 8 weeks. Patients who have urine protein ≥ 300 on U/A should have a random UPC ratio checked for pazopanib patients only.

- Patients on Pazopanib will have serum chemistry and electrolytes including total protein, albumin, alkaline phosphatase, AST, ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, sodium, potassium, chloride, and carbon dioxide will be done every 2 weeks for the first 8 weeks and 8 weeks x 2, and every 16 weeks therafter. Pazopanib patients will have CBC with platelet count and differential every 2 weeks for the first 8 weeks, every 8 weeks x 2, and every 16 weeks thereafter.

- Patients on temsirolimus will have serum chemistry and electrolytes including total protein, albumin, alkaline phosphatase, AST, ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, sodium, potassium, chloride, and carbon dioxide will be done every 2 weeks for the first 8 weeks and every 4 weeks thereafter. Fasting lipid panel every 4 weeks for the first 8 weeks, every 8 weeks x 2, and every 16 weeks thereafter. CBC with platelet count and differential will be done every week for patients on temsirolimus.

- Record concomitant medications with each history and physical.

- Reconcile the medication diary provided during treatment with each history and physical for those on pazopanib.

- Adverse events will be assessed at each visit and monitored throughout the study.

- 12-Lead Electrocardiogram will be repeated at Cycle 2 Day 1, 12 weeks later, and every 16 weeks after that for patients on Pazopanib. (see Section 6.1.1.4 for additional details of QT interval monitoring) Patients receiving temsirolimus will have an ECG done every 16 weeks.

- Optional blood specimens for future correlative studies will be obtained every 8 weeks and at progression.

- Serum amylase and lipase will be obtained only as clinically indicated.

- Serum T4 and TSH will be obtained every 8 weeks for patients receiving pazopanib.

- Repeat radiological studies (CT, MRI as indicated) to evaluate response every 8 weeks. Studies to confirm a complete response or document progressive disease will be performed as needed. Patients who are progression free after 1 year can have their imaging studies obtained every 16 weeks.

- Echocardiogram or MUGA scan (echocardiogram preferred) will be repeated every 24 weeks and as clinically indicated.

Outside Physician Participation During Treatment (Temsirolimus Patients may have interim infusions with local MD)

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix J); A copy of the protocol abstract and evaluation during treatment will be provided to the local physician with the letter.
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
6. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
7. Patients will return to MDACC every 8 weeks for evaluation.

8. Patients on pazopanib/torisel who have reached 12 months without progression may see their local physician and will return to MDACC every 8-16 weeks for evaluation and restaging.

5.5 Off Treatment Follow-up (30 days after stopping therapy)

Attempts will be made to follow-up with the patient in 30 days after the last dose of study drug. If a patient cannot return for the 30-day assessment and contact cannot be made due to disease progression, inability to return, hospice care, death, etc, this will not be considered a protocol deviation. Reporting to the IRB for deaths and other serious adverse events will be performed.

- Record concomitant medications.
- Adverse events will be assessed
- Optional blood draw for correlative studies

5.6 Crossover Phase

- At progression by RECIST, if they have not suffered an adverse event that would preclude them from continuing with systemic therapy and after the applicable washout period, of 2 weeks, patients who continue to meet the eligibility criteria will begin treatment with the remaining agent.

  Note:
  - At the discretion of the treating physician, the patient may continue on their 1st-line agent if the treating physician believes the patient is benefitting, despite progression by RECIST.
  - Patient may start their 2nd-line therapy within 2 weeks from the last dose of the agent given in 1st-line, if felt indicated by the treating physician.
  - Patients who develop progressive disease while receiving the 1st-line agent may receive radiation therapy or undergo surgery if indicated and continue to receive treatment on protocol, as long as the 2nd-line agent is commenced within 8 weeks from discontinuation of the 1st-line agent.

- For the cross-over stage of the study, patients will repeat the schedule of assessments as provided in the study calendar and section 5.4. Cardiovascular assessments will only be repeated if more than 24 weeks from the previous exams and only for those who'll be receiving pazopanib. A MRI/CT of the brain will be performed at crossover to rule out any progression before the start of crossover therapy at the discretion of the physician.

- Screening blood work must have been performed within the past 14 days before starting the new treatment.

- Optional blood draws will continue the same schedule as indicated in the study calendar.

5.7 Long-Term Follow-up

Patients will be followed for overall survival every 3 months after removal from final study therapy. Follow-up will consist of a phone call, e-mail correspondence or medical record review.

5.8 Supportive Care

The use of concurrent medications and blood products will be left to the discretion of the treating physician and should follow established guidelines.

5.9 Duration of Therapy

Patients may continue therapy until progressive disease by RECIST criteria or until other criteria for removal (Section 12) has been met.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 General Guidelines

Doses will be delayed or reduced for clinically significant hematologic, renal, and other toxicities that are related to pazopanib or temsirolimus, as determined by the investigators at MD Anderson. All toxicity will be assessed using the NCI CTC version 4.0. Recovery from any toxicity to at least grade 1 or baseline as outlined below must occur prior to re-initiating therapy with agent responsible for the toxicity. Treatment with the same agent will resume as soon as possible with the appropriate dose reductions. Patients receiving treatment who experience an adverse event that necessitates its interruption and a delay of ≥ 6 weeks in its re-initiation will discontinue it and come off protocol. In all cases, patients, who are withdrawn from the study due to adverse event(s), must be followed until resolution of the adverse event(s) or start of new treatment. If a patient experiences several toxicities leading to conflicting recommendations, the recommended dose adjustment reducing the dose to the lowest level will be used. The dose of any study drug may be re-escalated to a higher level following discussion with the principal investigator. All dose modifications will follow predefined dose levels.

Patients who require any emergency intervention (e.g. for appendectomy or cholecystectomy because of trauma complications) or who require a procedure (e.g. Kyphoplasty/vertebroplasty) may remain on trial, even if administration of the targeted agent is interrupted, as long as the targeted agent is resumed within 6 weeks from date of interruption.

<u>Pulmonary Embolism</u>

Patients who are incidentally discovered on CT scan imaging to have pulmonary embolism may receive anticoagulation and continue treatment on protocol at the discretion of the treating physician.

6.1.1 Pazopanib Dose Modifications

Dose Modifications for Pazopanib Associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematological	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment with the dose reduced by 1 level	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment with the dose reduced by 1 level
Hematological	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level

Dose Level	Pazopanib
0	800 mg oral Daily
-1	600 mg oral Daily
-2	400 mg oral Daiily

6.1.1.1 Guidelines for Management of Treatment Emergent Hepatotoxicity

In the event of treatment emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis, choledocholithiasis, and hepatic metastases should be investigated. Concomitant medications known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, ALT >3x ULN and concomitant bilirubin ≥2.0xULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury. The table below provides guidelines for hepatotoxicity monitoring.

Event	Dose Modification Algorithms
(A). ALT ≤ 3.0 x ULN	Continue study treatment at current dose with LFTs monitored as per protocol.

(B). ALT >3.0 x ULN to ≤8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	Liver Event Monitoring Criteria: (1) Continue study treatment at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs once 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 <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	1st occurrence – Liver Event Interruption Criteria: (1) Interrupt treatment until toxicity resolves to ≤Grade 1 or baseline. Repeat liver chemistries within 24 to 72 hours. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs once weekly or more frequently if clinically indicated until ALT is reduced to Grade 1. (4) If the subject is benefiting from the study treatment, consider re-challenge. Re-treatment may be considered at a dose of 400 mg once daily and with weekly serum liver tests x 8 weeks, if ALL following criteria are met: - ALT 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: Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs once weekly or more frequently if clinically indicated until ALT is reduced to Grade 1.
(D). ALT >3.0 x ULN with concomitant elevation in bilirubin2 (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash)	Liver Event Stopping Criteria: (1) Discontinue treatment immediately, and report the event to Novartis as an SAE within 24 hours of learning of its occurrence. Repeat LFTs within 24 hours. (2) Consult a gastroenterologist / hepatologist, 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, anti-mitochondrial antibody - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation

	- Liver imaging (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 weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin 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 >2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue pazopanib at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

1. Full panel LFTs include: AST, ALT, alkaline phosphatase, , and total bilirubin.
2. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2.0 x ULN, then the event should be promptly reported as defined.
3. When a liver chemistry event meets the Liver Event Interruption Criteria, or Liver Event Stopping Criteria, blood samples should be obtained for clinical laboratory testing.

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; LFT liver function tests; SAE serious adverse event; ULN upper limit of normal.

6.1.1.2 Guidelines for Management of Treatment Emergent Hypertension

Hypertension Grade of Event per MDACC guidelines	**Management/ Next Dose**
Grade 1	Consider increased BP monitoring
Grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue agent

requiring more than 3 antihypertensive medications.	
Grade 2 symptomatic/ persistent OR diastolic BP ≥ 110 mm Hg OR grade 3	1. Agent should be held until symptoms resolve and diastolic BP ≤ 100 mm Hg; also treat patient with anti-hypertensives and when agent is restarted, reduce by 1 dose level. Following discussion with the PI, determination to continue with same dose or reduce by 1 level may be made. 2. If diastolic BP not controlled (≤ 100) on maximal medical therapy (as defined as more than 3 antihypertensive medications), reduce one dose level
Grade 4	Discontinue the offending agent and remove patient from

MDACC Hypertension definitions:
Grade 1: asymptomatic, transient (< 24 hours) increase > 20 mmHg (diastolic) or to >140/90 if previously WNL; intervention not indicated
Grade 2: recurrent or persistent (>24 hours) or symptomatic increase > 20 mmHg (diastolic) or to >140/90 if previously WNL; monotherapy may be indicated.
Grade 3: requiring multiple antihypertensive agents or more intensive therapy than previously
Grade 4: life-threatening (e.g., hypertensive crisis)

6.1.1.3 Concomitant Strong CYP3A4 Inhibitors:

The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations and should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of pazopanib to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.

6.1.1.4 12-Lead Electrocardiogram

In clinical studies with pazopanib, events of QT_cB prolongation have occurred. For patients receiving pazopanib a 12-lead ECG will be obtained at Screening/Baseline and again at Cycle 2 Day 1. If QT_cB is normal, patients will have an ECG every 16 weeks thereafter. Prior to each ECG test, the subject should be at rest for approximately 10 minutes.

If the QT_cB interval at any ECG during treatment is ≥ 500 msec, study drug will be held and the ECG should be repeated within 7 days and, if the QT_cB interval remains

≥ 500 msec, the subject should be removed from the study. The ECG can be performed at an outside facility with results sent to MDACC.

Additionally, if the QT_cB interval is increased by 60 msec or more from baseline, but the QT_cB interval remains at < 500 msec, an ECG should be repeated within 7 days. If the repeat ECG again shows a ≥ 60 msec increase in the QT_cB interval from baseline, consideration should be given to removing the subject from the study or increasing monitoring, after discussion with the principal investigator.

NOTE: If the QT_cB prolongation > 500 msec is clearly and causally associated with an underlying situation that is clearly reversible (e.g., a subject with severe diarrhea and hypokalemia with QT_cB prolongation that resolves once the diarrhea improves and potassium is corrected), then the subject may restart study drug once the underlying situation has been corrected (e.g., electrolytes supplemented), the QT_cB interval prolongation has resolved.

6.1.2 Temsirolimus Dose Modifications

6.1.2.1. Hepatic Impairment: Use caution when treating patients with hepatic impairment. If temsirolimus must be given in patients with mild hepatic impairment (bilirubin >1 – 1.5 x ULN or AST >ULN but bilirubin ≤ULN), reduce the dose of temsirolimus to 15 mg/week. Temsirolimus is contraindicated in patients with bilirubin >1.5 x ULN .

6.1.2.2. Hypertriglyceridemia
Patients who have persistently elevated serum triglycerides (> 1000mg/dL) for ≥ 4 weeks, despite treatment with lipid-lowering agents, or patients who develop pancreatitis (regardless of the duration of the preceding triglyceride elevation) should discontinue temsirolimus and come off protocol.

Temsirolimus should be held for absolute neutrophil count (ANC) < 1,000/mm^3, platelet count< 75,000/mm^3, or NCI CTCAE grade 3 or greater adverse reactions. Once toxicities have resolved to grade 1 or less, temsirolimus may be restarted with the dose reduced by 5 mg/week to a dose no lower than 15 mg/week.

6.2 Concomitant Drugs

Patients receiving both pazopanib and temsirolimus will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug. All concomitant

medications/significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded. Please reference the Warnings and Precautions section for CYP3A4-related drugs in the temsirolimus label and the Dose Modification Guidelines section in the pazopanib label for further detail.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- It is highly recommended that patients with positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug.
- The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule.

Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided

No chronic treatment with systemic steroids (at a dose equivalent of greater than 20 mg prednisone per day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with temsirolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

7.0 QUALITY OF LIFE ASSESSMENT

Measuring quality of life (QOL) outcomes in cancer patients has become an important mandate for clinical trials. It is especially important to assess QOL in phase II cancer clinical trials that are likely to move into the phase III setting. The extent to which treatment impairs QOL is information the patients need when making treatment decisions.

Patients will experience somewhat different symptoms when they receive the different therapies. In order to assess the effects of these treatments, we will assess multidimensional aspects of QOL over the treatment course.

<u>Assessment Schedule</u>

All patients will complete a full assessment battery at baseline, prior to treatment. Patients will then complete an assessment battery every 8 weeks when they come in for their clinical evaluation (see Table 1).

Table 1: Data collection sessions for psychosocial measures

BASELINE	**FOLLOW-UP** (EVERY 8 WEEKS)
• FACT-G • FKSI-15 • Depression (CES-D)	• FACT-G • FKSI-15 • CES-D

Instruments

Several measures used previously in our work on chronic stress and QOL will be used in the proposed study. In all cases, they have proven to be useful and sensitive measures of stress and QOL, have proven to be stable, reliable, and valid with groups of people who are and are not suffering from major depression or other psychiatric disorders.

Quality of Life

The Functional Assessment of Cancer Therapy (FACT) is a cancer-specific measure of health-related quality of life. This instrument was able to discriminate between individuals with metastatic and non-metastatic disease, as well as between patients at different stages of illness. The scale has been found to have good concurrent validity, high internal consistency (0.89), and good test re-test reliability (0.82 to 0.88). The FACT will be completed at each assessment. Kidney cancer specific QOL symptoms will be assessed with the FKSI-15 from the FACT group.

Depression:

Depression will be assessed using the Centers for Epidemiologic Studies - Depression (CES-D). The CES-D is a well-validated 20-item self-report measure of depression that focuses on affective components of depression. Cut-off scores of 16 for screening clinical depression have been recommended. Internal consistency is high in the general population and in patient populations. It also has been demonstrated to possess adequate convergent validity with other measures of depression. The CES-D will be completed at baseline and at each subsequent clinical visit (every 8 weeks).

8.0 CORRELATIVE STUDIES

Optional blood will be collected on day 1 of cycle 1, day 1 of every other cycle, and at the end of treatment. Blood will be stored in the GU Biorepository and tissue will be stored in the MD Anderson institutional tissue bank.

We plan to identify and quantify circulating endothelial cells (CECs) in peripheral blood. We hypothesize that CECs correlate with tumor angiogenesis in mRCC and may thus be useful for the monitoring of disease progression. Moreover, we expect to find treatment-related effects on CECs, which could contribute to the assessment of response in future studies with anti-angiogenic therapies. The presence

of a dynamic number of CECs in the circulation of cancer patients is already well established. Recent reports suggest a role for CECs as biomarkers of cancer progression and response to targeted therapies. Two distinct populations of CECs have been identified: Circulating endothelial progenitor cells, mainly derived from bone marrow, which may contribute to the formation of new blood vessels in the tumor; and mature CECs, thought to be derived from established vasculature. In addition to immunophenotypic markers like CD146, CD133, VEGFR2 and CD31, both populations can be distinguished by a distinctive ability for proliferation. We will obtain a mononuclear cell fraction from each blood specimen and detect CECs by fluorescence-activated cell sorting analysis. We will systematically examine changes in the plasma and serum angiogenic profiles consisting of a panel of pro-angiogenic cytokines, targeted receptors, and potential biomarkers of endothelial damage.

The analysis of plasma- and serum-based biomarkers will focus on two groups of proteins. First, factors known to be modulated by VEGFR antagonists or by endothelial injury will be assessed. Such biomarkers include plasma VEGF and soluble VEGFR-2, as well as soluble VEGFR-1 and E-selectin.

The second set of factors will be pro-angiogenic cytokines that may contribute to resistance to VEGF inhibitors by promoting the proliferation and survival of tumor endothelial cells even in the presence of VEGF blockade. These cytokines will be assessed in two ways. First, several selected pro-angiogenic cytokines known to play a role in angiogenesis in renal cell cancer, including VEGF, basic fibroblast growth factor (bFGF), transforming growth factor α (TGFα), and interleukin-8 (IL-8), will be assessed quantitatively by validated enzyme-linked immunosorbent assay (ELISA). Second, we will broadly screen a set of approximately 100 known angiogenic factors by using an established cytokine array capable of detecting angiogenic factors. Candidate cytokines identified using the array will then be assayed individually.

Plasma VEGF levels will be measured using commercially available ELISA kits. VEGF levels can be accurately detected at a level of 6–20,000 pg/ml with a coefficient of variance of less than 10% by this method. TGFα, bFGF, IL-8, and other soluble factors will be analyzed using similar methodologies. Together with the cytokine array, these assays will form an angiogenic profile that will be monitored during treatment and at time of disease progression.

We will also use these assays to find correlations with adverse events. Our hypothetis is that cardiovascular toxicity may be related to baseline levels and/or changes of inflammatory cytokines, angiogenic factors, or markers of endothelial damage or repair.

Immunological studies will be conducted to define changes in effector and regulatory T cell populations and/or function and changes in cytokine profiles that occur after patients have started treatment. Laboratory techniques will follow previously published methods and will include flow cytometry, ELISA assays, ELISPOT assays, Affymatrix analyses, microRNA analyses, Western blot and reverse-phase protein array analyses. 90 cc of blood will be collected pre-therapy at baseline, at 8 weeks and 16 weeks, and at progression. Blood will be processed by standard ficoll methods and immunological studies will be conducted on obtained PBMCs and plasma.

When feasible, pre-treatment tissue samples leftover from routine diagnostic procedures will be collected for the proposed correlative studies. In addition, residual pathological material may be collected for patients who undergo procedures while on therapy. Specific biological markers will be

assayed, focusing on factors associated with angiogenic signaling, and the activity and viability of specific cell types within the tumor, including the MAP kinase pathway, and the PI3K pathway with a focus on signaling molecules downstream of mTOR. A tissue microarray will be generated from nephrectomy or metastasectomy blocks from patients enrolled on the trial. For patients where blocks are not available selected staining may be performed on biopsy material where indicated. Specifically, to evaluate the MAP kinase and PI3K pathways, ERK, phospho ERK, p38, phospho p38, Akt phospho Akt, S6 kinase, phospho S6 kinase S6, phospho S6 and EIF4E and VEGF isoforms will be assayed using immunohistochemical techniques. In addition, p27 levels and its subcellular localization, Ki67 levels, and the TUNEL assay will be performed to evaluate the effect of temsirolimus and pazopanib on cell cycle, proliferation and apoptosis in endothelial, stromal and tumor cells. Other biomarkers may be added as appropriate to contextualize the information gathered from the above assays. To assess the effect of temsirolimus and pazopanib on angiogenesis, endothelial FGFR, VEGFR2, Tie-2 and PDGFR levels and phosphorylation states will be assayed using coimmunofluorescence techniques. In addition, we will also evaluate the potential effect of temsirolimus, and pazopanib on the expression of TGF-α, which has been suggested to be a prognostic factor in RCC patients, and may increase RCC growth via an autocrine loop. Oligonucleotide array analysis will also be performed to detect global patterns in pre-treatment tumor samples. Since chromosome copy number alterations have been shown to be associated with outcomes of clear-cell RCC, we will determine whether chromosomal imbalances identified with SNP arrays could be used as predictors of response to these agents. We will obtain archival FFPE tumor samples and extract DNA from the FFPE tissue sections for analysis with Affymetrix 250K Nsp SNP microarrays to identify genomic imbalances and loss of heterozygosity (LOH) (Samples will be sent to Dr. Federico Monzon at Baylor College of Medicine for SNP Analysis, please see Appendix G for procedural details).

By performing these studies, we aim to generate correlative information that will permit improved therapeutic applications in the future.

We also aim to evaluate the loss of SETD2 histone methyltransferase activity, its effect on the decreases of H3K36 trimethylation (H3K36Me3) and the possible promotion of tumorigenesis in RCC. (Samples will be sent to Dr. Thai Ho at Mayo Clinic – Scottsdale, AZ for analysis, please see Appendix H for procedural details.)

9.0 STUDY CALENDAR

In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. All evaluations will have a standing window of allowance equal to +/- 3 days.

	Screening	Weekly	Every 4 Weeks	Every 8 Weeks	Every 16 Weeks	Off Treatment [q,r]
History & Physical Exam	x[a]		x[p]	x[h]		
Concomitant Meds	x[a]		x[p]	x[h]		x
Vital Signs incl. Weight	x[a]	x[b]	x[p]	x[h]		
Height	x[a]					
Performance Status	x[a]					
CBC w/ Dif & Plts.	x[a]	x[e,p]	x[e]	x[e]		
Serum Chemistry[d]	x[a]	x[s]	x[s]	x[h,s]	x[h,s]	
Lipid Panel	x[a]		x[e]	x[e]	x[e]	
Amylase	x[a, f]		x[f]			
Lipase	x[a, f]		x[f]			
PT/PTT	x[a]					
ßHCG[g]	x[a]					
Free T4 & TSH [h]	x[a]			x[h]		
Urinalysis	x[a]			X[h,i]		
Radiological Evaluation[j]	x[k]			x	X[t]	
Electrocardiogram	x[k]		x[f,n]		x[p]	
Echocardiogram or MUGA scan	x[m]		Repeated every 24 weeks			
	Screening	Every 8 weeks off treatment				
Adverse Event Monitoring		Adverse Events will be monitored throughout				
Quality of Life battery	x[a]			x		
Optional Blood Collection[l]	x[a]			x		x

Optional Tissue Collection[c,o]	←---------→

a. Within 14 days of registration
b. Only the blood pressure must be monitored weekly for the 1st 4 weeks on study in patients receiving pazopanib. This may be performed at a doctor's office or using any calibrated electronic device.
c. Previously collected tissue, will be requested from patients who consent. This tissue may come from MD Anderson or an outside institution. Tissue will be requested, once the study is closed to new patient entry, to allow for batch analysis. No new procedures will be required. This tissue will also be banked for future research related to immunologic response.
d. Serum chemistry consists of total protein, albumin, alkaline phosphatase, AST and ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide.
e. CBC with platelet count and differential will be done every 2 weeks for the first 8 weeks,every 8 weeks x 2, and every 16 weeks thereafter, for patients on pazopanib. For patients on temsirolimus, a CBC with platelet count and differential will be done weekly. Fasting lipid panel will be done every 4 weeks for the first 8 weeks, every 8 weeks x 2, and every 16 weeks thereafter, for those patients receiving temsirolimus .
f. As clinically indicated
g. Female patients of child-bearing age must have a negative pregnancy test within 7 days of beginning treatment.
h. Patients receiving pazopanib only
i. Urinalysis. If patient has urine protein $\geq$ 300 on UA, a random UPC ratio should be ordered.
j. CT Chest, abdomen and pelvis. MRI of the brain (bone scan, plain films) should be obtained as appropriate. MRI of the abdomen and/or CT scan of the brain can be substituted at the physician's discretion.).
k. Within 4 weeks of study entry
l. Optional blood collection for future correlative studies will be drawn at baseline, every 8 weeks, and at Off Treatment Visit.
m. Within 12 weeks of study entry
n. Patients receiving pazopanib will have a follow-up ECG at C2D1, 12 weeks later, and every 16 weeks thereafter.
o. Tissue will also be collected during procedures performed, at any time point, while patients are enrolled in this study. No new procedures will be required. This tissue will also be banked for future research related to immunologic response.
p. Patients receiving temsirolimus
q. In 30 days after stopping therapy
r. Long-Term Follow-Up for survival will occur every 3 months from final study therapy. Follow-up will consist of a phone call, e-mail correspondence or medical record review.
s. Every 2 weeks for the first 8 weeks (both arms). Temsirolimus patients every 4 weeks thereafter. Pazopanib patients every 8 weeks x 2 and every 16 weeks thereafter.
t. Patients who are progression free after 1 year can have their imaging studies obtained every 16 weeks.

10.0 CRITERIA FOR RESPONSE AND PROGRESSION

10.1 Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the

RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

10.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). In patients with primary tumor in place, the primary tumor will not be considered a site of measurable disease.

10.1.2 Non-measurable disease

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

10.1.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

10.1.4 Non-Target Lesions

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

10.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

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

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

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

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

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

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

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

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.

10.3 Response Criteria

10.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

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

10.3.3 Evaluation of Best Overall Response

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

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

Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.4 Confirmatory Measurement/Duration of Response

10.4.1 Duration of overall response

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

10.4.2 Duration of Stable Disease

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

11.0 Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 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

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board (IRB) Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". For this protocol adverse events will be captured according to the Recommended Adverse Event Recording Guideline for Phase II protocols (below).

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II	Phase I Phase II

				Phase III	Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported In accordance with the IRB policy. This may include the development of a secondary malignancy.**

Reporting to FDA:

- SAE's will be reported per regulatory (local and federal) guidelines.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the supporter guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

Reporting to Novartis for patients taking Pazopanib

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 at least 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: 877-778-9739) 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.

12.0 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT

Subjects who meet the following criteria should be discontinued from study treatment:

- Progressive disease: Patients, who develop rapidly progressive disease before the scheduled evaluation, may be taken off study at the discretion of the investigator, if they are not felt to be candidates to begin treatment with the second agent.
- Intercurrent illness that, in the opinion of the treating physician/investigator, prevents continuation of treatment.
- Decision of the patient to withdraw from the study, or patient non-compliance with therapy.
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
- Any grade arterial thromboembolic event
- Grade 4 congestive heart failure
- Gastrointestinal perforation
- Wound dehiscence requiring surgical intervention

13.0 STATISTICAL CONSIDERATIONS

This is a randomized, two-arm, parallel group, phase II trial enrolling advanced, poor-risk, clear-cell RCC. Patients will be fairly randomized to either temsirolimus (control arm) or pazopanib (experimental arm).

The maximum sample size to be accrued is 90 patients (45 in each treatment arm). The primary measure of efficacy and primary endpoint is progression free survival (PFS). PFS will be monitored on an interim basis and we will use stopping rules for futility to serve as guidelines for early termination. The stopping rules are ad-hoc in nature but are selected in a manner such that the overall type 1 error is controlled at a one-sided 10% with 80% power.

Descriptive and inferential statistics will be used to summarize treatment effects. The mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported for continuous variables. For discrete variables, descriptive analyses will be based on the distribution of discrete outcomes and will be reported as percentages and patient counts. Time to event endpoints will be descriptively summarized by Kaplan-Meier curves. Point and interval estimates of treatment effect will be based on maximum likelihood methods. For binomially distributed variables, we will report differences in proportions between treatment groups and the 95% confidence interval associated with those differences. We will estimate treatment effects for time to event variables via hazard ratios using Wald scores from Cox proportional hazard regression models. Unless stated otherwise, all statistical tests will be assessed using a two-sided a= 0.05 alpha significance level and confidence intervals will be constructed using two-sided 95% and will be based on the normal approximation. Although multiple secondary endpoints will be evaluated we will make no adjustment for multiplicities associated with these multiple tests.

Estimation of Sample Size

The clinical hypothesis we are assessing in this trial is whether patients receiving the experimental therapy have a lower hazard of progression or death relative to patients receiving the control therapy. The statistical hypothesis is stated as:

$$H0: \quad \log(HR)=0$$

$$HA: \quad \log(HR)<0$$

Where HR is the hazard ratio (experimental:control). For sample size calculation purposes we assume that the median PFS in the temsirolimus arm is 60% that of the pazopanib arm (3.8 months versus 6.1 months). The sample size estimate is based on a one-sided log-rank test with type one error equal to 0.10 and power of 0.80.

We will conduct an interim analysis for futility after 42 events have been observed. If the p-value used to assess futility at the interim analysis is greater than 0.4798 we will stop the trial early for futility.

Secondary Objectives

Overall survival: Overall survival is calculated from day of therapy initiation to the date of death. Patients who are lost to follow-up will be censored at date of last contact.

We will use the Kaplan-Meier estimator to estimate the OS for each group of patients (control, experimental), and the log-rank statistic will be used to test for treatment differences. We will also use the Cox proportional hazards regression model to estimate the hazard ratio (experimental:control) for OS with a 95% confidence interval.

We will also assess the response rate and report 95% confidence intervals.

Additional analyses:

Demographics

For each treatment group (control, experimental), summary statistics will be provided for age, weight, baseline disease status and prior treatments.

Toxicities

Toxicities and side effects that will be evaluated include, but are not limited to infections, renal toxicity, hepatic toxicity, and pulmonary toxicity. Methods of assessment will include monitoring blood counts, and performing laboratory tests as indicated by clinical signs and symptoms. Evidence of toxicities or adverse events will be recorded at all clinic visits. All observed toxicities and side effects will be graded (NCI CTC-AE v. 4.0) for all patients and the degree of association of each with pazopanib or temsirolimus assessed. The incidence and severity of toxicities will be compared between the two treatment arms with Fisher's exact test.

Stratification Factors

The Pocock-Simon Minimization Method will be used to randomize patients according to the following stratification factors:

- Prior nephrectomy status (yes or no)

- Prior cytokine/vaccine therapy (yes or no)

The randomization program based on this method will be developed in the Department of Biostatistics and Applied Mathematics, and the program will be available via an intranet web site of MD Anderson Cancer Center.

Data Analyses for Quality of Life Measures

Prior to inferential procedures, extensive descriptive analyses will be conducted for each of the measures obtained at each session. Descriptive statistics (e.g., means, ranges, standard deviations) will be computed, together with ninety-five percent confidence intervals for the means. Proportions of subjects falling outside normative ranges for the stress and QOL measures will also be calculated. Values for the standardized scales will be compared to normative data and patients receiving other types of cancer therapy. Graphical methods (e.g., boxplots and histograms) will be employed to more closely examine the distributions of the

measures at each time point. Change scores for the stress and QOL measures will be computed as the simple differences between the baseline measure and subsequent evaluations. Bivariate associations between the raw scores, the change scores, optimism, social support, and demographic variables will be evaluated using Pearson's product moment correlation coefficients together with scatterplots where appropriate. These procedures will allow us to thoroughly characterize the stress and QOL profiles of this patient population across the sessions.
In this study, numerous models will be constructed to analyze the data and, therefore, the results will be treated as hypothesis generating and interpreted with caution. Inferential statistics will comprise paired t-tests of the stress and QOL measures. Significant test results ($p < .05$) will be interpreted as indicating significant changes in depression and QOL associated with the treatment. The association between depression and survival and TTP will also be examined.

14.0 REPORTING AND EXCLUSIONS

14.1 Evaluation of toxicity**:**

Patients will be evaluable for toxicity related to the targeted therapy given in the first stage and in the second stage.

14.2 Evaluation of response**:**

All patients who are registered and assigned to treatment will be assessed for response.
All patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients with an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-8 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. Data analysis will be performed using SAS or S-Plus, as appropriate. Patients who die of unrelated cause during therapy or are lost to follow-up shall be censored.

15.0 DATA AND PROTOCOL MANAGEMENT

15.1 Protocol Compliance

The attending physician or designee will see each patient for evaluation of tumor response and toxicity every 8 weeks. All required interim and pretreatment data should be available, and the physician must make a designation as to tumor response and must provide a detailed description

of toxicity, when appropriate. If dose modifications or treatment interruptions are necessary, the details must be carefully documented.

15.2 Data Entry

Data will be entered into the GURU database at MD Anderson Cancer Center. GURU is a password protected database with an audit trail. Data can be collated with a unique GURU identification in order to de-link information.

15.3 Accuracy of Data Collection

At an appropriate time, an independent panel of hired radiologists will review all imaging studies to assess progressive disease and response in each patient, but the principal investigator at each institution will be responsible for decision regarding the treatment phases of each patient on this trial.

15.4 Study Drug Destruction

The institution will destroy any supplies of investigational product and other study medications that expire during this trial, as well as all supplies that remain unused at the termination of this trial. Institution will destroy these materials in accordance with all applicable regulations, governmental guidelines, and institutional policies.

16.0 INVESTIGATOR OBLIGATIONS

16.1 Review for institutional review as set forth in 21 CFR, Part 56 will be followed. Requirements for informed consent as set forth in 21 CFR, Part 50, will be followed. The investigator will keep the IRB informed as to the progress of the study as well as to any serious or unusual adverse events.

16.2 All protocol amendments and consent form revisions will be reviewed and approved by the MDACC IRB prior to implementation. Any change to the protocol intended to eliminate any immediate risk to patients may be implemented immediately, but IRB must be notified at the time and a protocol amendment must subsequently submitted for approval.

Prior to initiation of therapy, the investigator will obtain a written informed consent from each patient, or their authorized representative, participating in the study. The consent form must be signed, witnessed and dated. The consent will contain all the essential elements of informed consent set forth in 21 CFR, Part 50.

16.3 Detailed case summaries will be generated for every patient from the database.

16.4 Patient Confidentiality: In order to maintain patient privacy, all database generated case report forms, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The patient's confidentiality will be

maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (21CFR312.63, 21CFR312.68). don't we have a better paragraph?

16.5 Record Retention: Study records include IRB approved protocol and informed consent, including historical copies of both, investigational drug brochure, signed informed consent forms, documentation of IRB approval, study forms, database-generated case report forms and source documents which allow verification of the case report forms. NO this needs to be more departmentally oriented.

17.0 REFERENCES

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3. Hurwitz HI, Dowlati A, Saini S *et al.* Phase I trial of pazopanib (GW786034), an oral multikinase angiogenesis inhibitor, in patients with advanced cancer: results of safety, pharmacokinetics, and clinical activity. *Clin. Cancer Res.* 15, 4220–4227 (2009).
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6. Sternberg CN et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28:1061–8.