Academic and Community Cancer Research United (ACCRU)

Randomized, Phase II Trial of Intravenous Ascorbic Acid (Vitamin C) as an Adjunct to Pazopanib in the First-Line or Post-immunotherapy Setting for Metastatic or Unresectable Clear Cell Renal Cell Carcinoma (ccRCC)

For any communications regarding this protocol, please contact the protocol resource person on the Protocol Resource Page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org).

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

Drug Availability
Commercial Agent: Pazopanib
Drug Company Supplied: ASCOR® - IND Exempt

Research Coordinating Center
Academic and Community Cancer Research United
[redacted]

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Index

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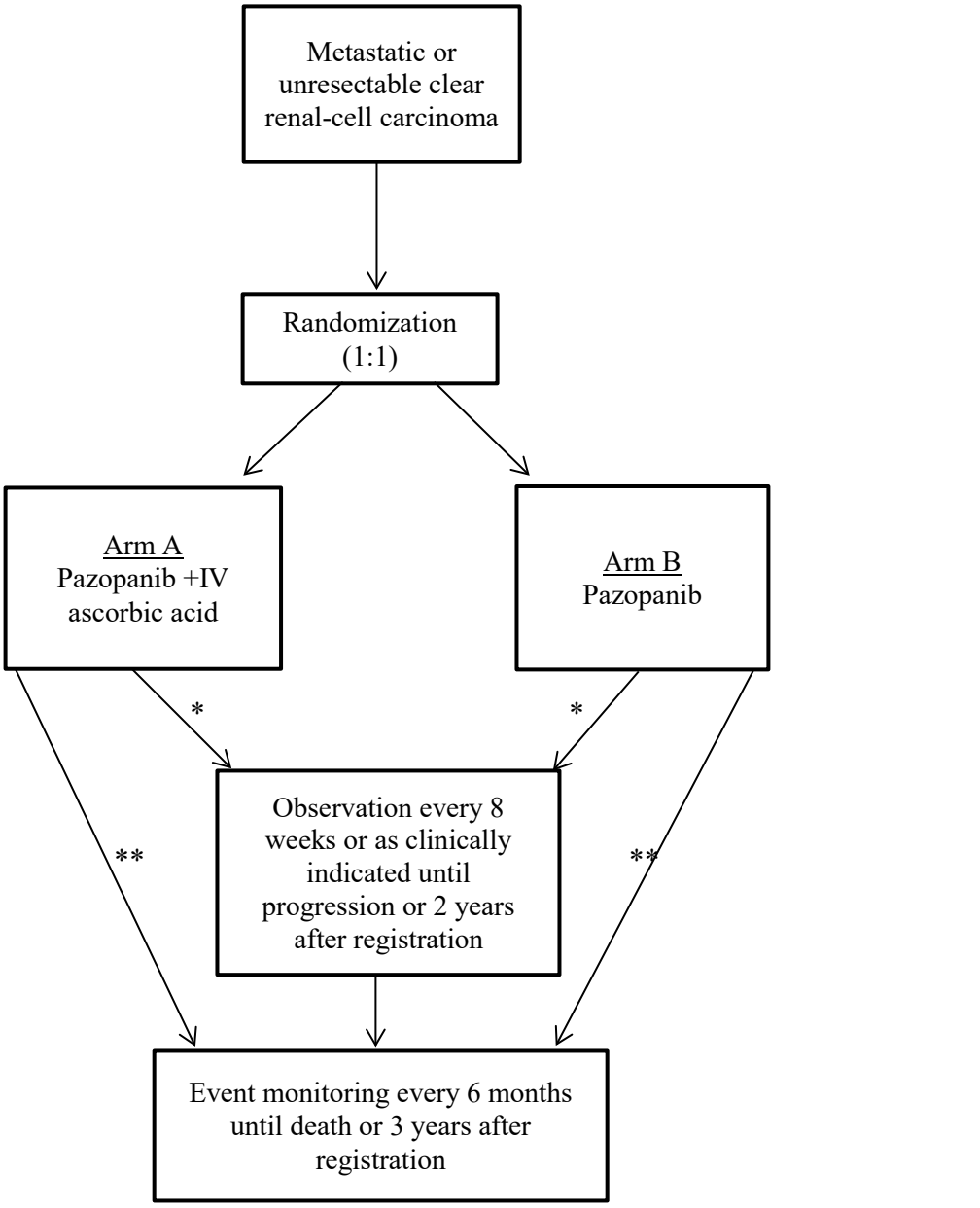
SCHEMA



*Off -treatment for any reason **other than** disease progression, alternative therapy, or withdraw/refusal
**Off-treatment due to disease progression, alternative therapy, or withdraw/refusal

1:1 Randomization
Arm A: Pazopanib 800mg daily plus intravenous ascorbic acid 1g/kg 3 times/ week.
Arm B: Pazopanib 800mg daily

Cycle = 28 days.

Patients receiving pazopanib, with or without IV vitamin C, will be treated for 10 cycles (unless PD, unacceptable AEs, alternative therapy, or patient refusal). Patients may continue pazopanib *after* 10 cycles (off study) based on physician discretion and patient acceptability.

Targeted patients: patients with metastatic / unresectable RCC, no prior treatment other than immunotherapy, who qualify for treatment with pazopanib.

Patients' disease status will be assessed by CT scan, per RECIST 1.1, every 8 weeks until disease progression, or until 2 years since study randomization, whichever is first.

In event monitoring, patients will be followed for survival every 6 months for a maximum of 3 years from study randomization. Once a patient has discontinued study treatment, future therapy is at the discretion of the treating physician.

Generic name: Pazopanib Brand name(s): Votrient® Availability: Commercially available	Generic name: Ascorbic Acid Brand name(s): Vitamin C, ASCOR® Availability: Clinical Research Services, a division of Rx Crossroads by McKesson

1.0 Background

Renal cell cancer (RCC) accounts for about 4% of all the adult malignancies. In the United States in 2016, about 61,560 cases of kidney cancer and renal pelvis cancer are expected to occur and lead to more than 14,080 deaths. The treatment options for metastatic RCC are limited. Tyrosine Kinase inhibitors (TKI) are considered to be the first line agents in metastatic RCC and provide a modest overall survival benefit.

Clear cell RCC accounts for about 80% of all RCC and the Von Hippel Lindau (VHL) tumor suppressor gene is mutated, deleted or epigenetically silenced in approximately 85% of sporadic clear cell RCC. Loss of VHL function leads to a constitutionally active Hypoxia Inducible Factor (HIF) pathway. The HIF pathway is considered to be the driver pathway in VHL mutant clear cell RCC.

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

Vitamin C has been used for many years as an oral anti-cancer agent. Although there were some studies that suggested benefit, oral ascorbic acid failed to demonstrate benefit in two randomized placebo controlled trials at the Mayo Clinic, [1, 2] after which mainstream oncologists discarded its role in cancer therapy. However, recent data on the pharmacokinetics of vitamin C and new understanding of its anti-cancer mechanism of action has led to resurgence in interest in exploring its potential in cancer therapy. These studies indicate that ascorbic acid at concentrations achieved only by the intravenous route functions as a pro-drug for hydrogen peroxide delivery to tissues and may have potential use in the treatment of cancer by induction of oxidative stress. [3-7] Phase 1 trials have demonstrated that intravenous ascorbate doses of up to 1-1.25g/kg are well tolerated with chemotherapy as well as targeted therapy, and there may be some anti-tumor activity.[8-10] It has also been shown to reduce the toxicity of chemotherapy. [11]

Clear cell RCC is an ideal model to test this hypothesis due to its characteristic high intratumoral iron content[12] and constitutionally active HIF pathway. We hypothesize that iron is an important component of the microenvironment to help ascorbate generate hydrogen peroxide; and it has already been shown that the constitutionally active HIF pathway renders ccRCC cells more susceptible to Vitamin C induced toxicity.[13] There have been case reports of excellent response of metastatic RCC with intravenous ascorbate.[14, 15] We propose testing the hypothesis in a randomized trial where patients will receive standard pazopanib either alone or with IV ascorbate.

Considering the impact of Mayo Clinic's studies on the use of vitamin C in cancer, we want to re-investigate the potential role of this agent in cancer therapy in the intravenous form, based on the accumulating evidence.

1.1 Mechanism 1

There has been a lot of debate whether ascorbic acid, which is traditionally considered a metal ion, ascorbic acid can readily undergo auto-oxidation to H2O2. Cancers have shown to increase ferritin levels. While we know that ferritin is an acute phase reactant, studies have demonstrated increased ferritin in the stroma of cancers. It is therefore believed that Fe3+ derived from the ferritin can act as a catalytic agent for the auto-oxidation of vitamin C, especially in high levels. Ascorbic acid therefore is believed to function as a prodrug of H2O2 in its anti-cancer activity. The large amounts of H2O2 produced can overwhelm the antioxidant defense mechanisms in the cancer cell. Cancer cells have been shown to usually have lower catalase, glutathione peroxidase and peroxiredoxin activity than normal cells, providing a rationale for the selective toxicity against cancer cells.[16-18] Even in the absence of catalytic metal ions, the H2O2 produced by oxidation of ascorbic acid is quite significant. There is also data suggesting that pharmacologic level of ascorbate can preferentially produce ascorbyl radical and H2O2 in the extracellular fluid [19, 20] Clinical proof of potent auto-oxidation of ascorbic acid and resulting pro-oxidant properties when given in large quantities, is the well documented case reports of intravascular hemolysis in patients with G6PD deficiency receiving large doses of intravenous vitamin C.[21, 22].

The following reactions are involved in the production of H2O2 with ascorbate:

1. Ascorbate reduces ferric ions (sequestered from ferritin) to ferrous ions

   AscH- (ascorbate) + Fe3+ → Asc*- (ascorbate radical) + Fe2+… (1)

2. The ferrous ions react with oxygen to form superoxide radical

   Fe2+ + O2 → Fe3+ + O2*- … (2)

3. Superoxide radical then dismutes to H2O2 and O2

   O2*- + O2*- + 2H+ → **H2O2** + O2 … (3)

The H2O2 formed can diffuse into cancers cells or, if the Fenton reaction takes place, more potent oxidants such as the hydroxyl radical (OH*) can be formed from H2O2 causing further oxidative stress in cancer cells, given have lower antioxidant machinery.

(Fenton reaction- Fe2+ + H2O2 → Fe3+ + HO* and the Fe3+ generated is reduced back to Fe2+ by ascorbate as in reaction 1).

Therefore, even though the eventual effect is that of a pro-oxidant with the generation of H2O2 and other oxidants, the first reaction involves anti-oxidant effect of ascorbate.

H_2O_2, which can diffuse into cells, depletes ATP in sensitive cells, and thereby cause cell death. ATP may be depleted by three mechanisms. (*i*) DNA damage induced by H_2O_2 activates PARP. Activated PARP catabolizes NAD^+, thereby depleting substrate for NADH formation and consequent ATP synthesis. (*ii*) H_2O_2 is catabolized by concurrent oxidation of GSH to GSSG. To reduce GSSG back to GSH, GSH reductase utilizes NADPH, which is provided by the pentose pathway shunt from glucose. Glucose used to reduce $NADP^+$ to NADPH cannot be used for glycolysis or NADH production so that ATP generation is decreased. (*iii*) H_2O_2 may directly damage mitochondria, especially ATP synthase, so that ATP production falls. Some cancer cells rely primarily on glycolysis rather than on oxidative phosphorylation respiration for ATP production (the Warburg effect). Compared with oxidative phosphorylation, ATP generation by glycolysis is inefficient. In glycolysis-dependent cancer cells, decreased glycolysis may lower intracellular ATP. Cancer cells that are glycolysis-dependent may be particularly sensitive to pharmacologic ascorbic acid concentrations, compared with cells that use oxidative phosphorylation.

In this mechanism, the extracellular production of H2O2 is important and not the intracellular concentration of Vitamin C. This mechanism however relies on the presence of iron or other catalytic metal agents for the anticancer activity and may explain, in part, the variability of the effect of intravenous vitamin C. Some cancer cells that have overexpression of catalase have been shown to be protected against vitamin C induced toxicity, further supporting this mechanism. [23]

In a fascinating study, RCC was shown to have abundant iron staining,[24] providing one rationale for using high dose ascorbic acid in RCC.

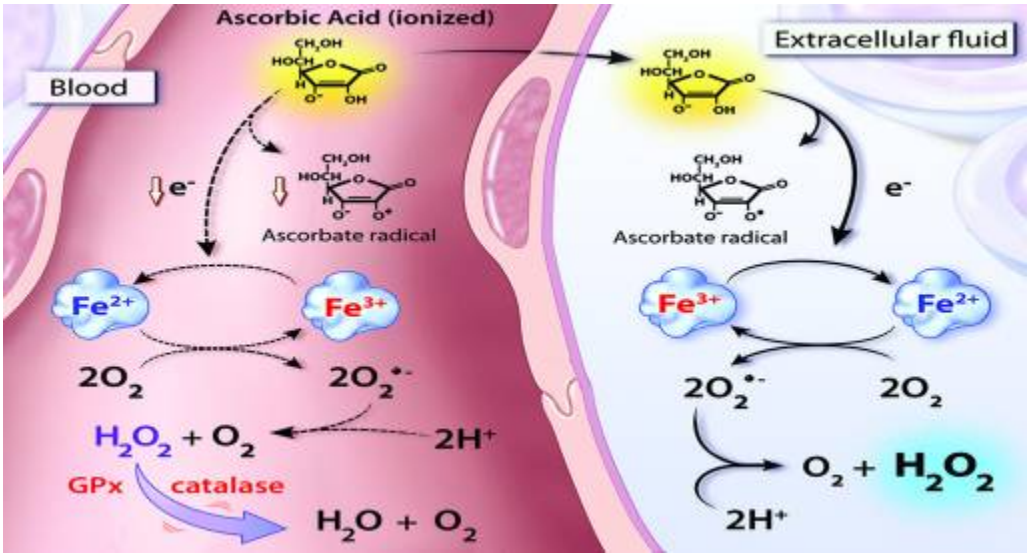


Fig1. Mechanism of formation of ascorbate radical and H_2O_2 in extracellular fluid compared with blood. After parenteral

administration, ascorbic acid achieves equivalent pharmacological concentrations in blood (left side of the diagram) and extracellular fluid (right side). In extracellular fluid, a molecule of ascorbic acid loses 1 electron and forms ascorbate radical. This electron subsequently reduces a protein-centered metal, shown as the reduction of Fe^{3+} to Fe^{2+}. This complex donates an electron to molecular oxygen, forming superoxide anion ($O_2\cdot^-$) with ensuing dismutation to H_2O_2. In blood (left side), these reactions are damped or inhibited (dashed lines). The appearance of ascorbate radical is inhibited by RBC membrane-bound reducing proteins and/or by large plasma proteins that do not distribute to the extracellular space. RBC enzymes glutathione peroxidase and catalase destroy whatever little H_2O_2 is produced in blood so that none is detectable in blood. The extracellular fluid H_2O_2 has been detected using a synthesized probe peroxyxanthone only after parenteral administration of ascorbate and when Asc (*-) concentrations in extracellular fluid exceeded 100 nM. (from ref 14). The ECF H_2O_2 formed then diffuses into cancer cells and causes ATP depletion and cell death (mechanism explained in text). The identities of the protein-centered metals are unknown- our hypothesis is that this could be the variable ferritin deposits in the tumor micro-environment. Tumor associated Macrophages are known to have high ferritin content and extracellular secretion of ferritin in the microenvironment is thought to play an oncogenic role.[25] We propose using the Prussian Blue reaction to detect loosely bound ferric ion in the tumor microenvironment, and correlating that with the response to IV ascorbic acid + TKI.

1.2 Mechanism 2:

To add to the above mechanism, it was recently shown that HIF increases the sensitivity of cancer cells to vitamin C induced toxicity. HIF increases the intracellular uptake of oxidized vitamin C (dehydroascorbic acid/ DHA) through its transcriptional target Glut 1 (which also transports glucose inside the cell). The resulting high levels of vitamin C induces oxidative stress, DNA damage and depletes ATP reserves leading to cell death.[26]. This study used VHL deficient RCC cell lines as well as VHL competent non RCC lines with high HIF activity. Inhibition of HIF activity with shRNA resulted in reduced Vit C induced toxicity and inhibiton of Glut 1 also had the same effect, further supporting this mechanism. This mechanism is particularly exciting given that the HIF is activated in many cancers especially in hypoxic areas and many cancers overexpress Glut1 as they rely on anaerobic glycolysis for their energy production. It is well known that Ascorbate (AscH-) is transported into the cell via sodium dependent Vitamin C transporters (SCVTs) but the expression of SCVTs in cells is tightly regulated by intracellular vitamin C concentration. Hence, beyond a certain point, transporting ascorbate into the cell is limited. However, Ascorbate, being a water soluble antioxidant, can undergo two consecutive, one-electron oxidations resulting in the formation of ascorbate radical (Asc^{*-}) and dehydroascorbic acid (DHA) and the DHA (i.e oxidized Vitamin C) is taken up without regulation via the Glut 1 receptors, resulting in oxidative damage and depletion of ATP stores (as all the NAD+ is used to

resolve the oxidative DNA damage, resulting in lesser availability for glycolysis, the main energy producing mechanism of cancer cells)

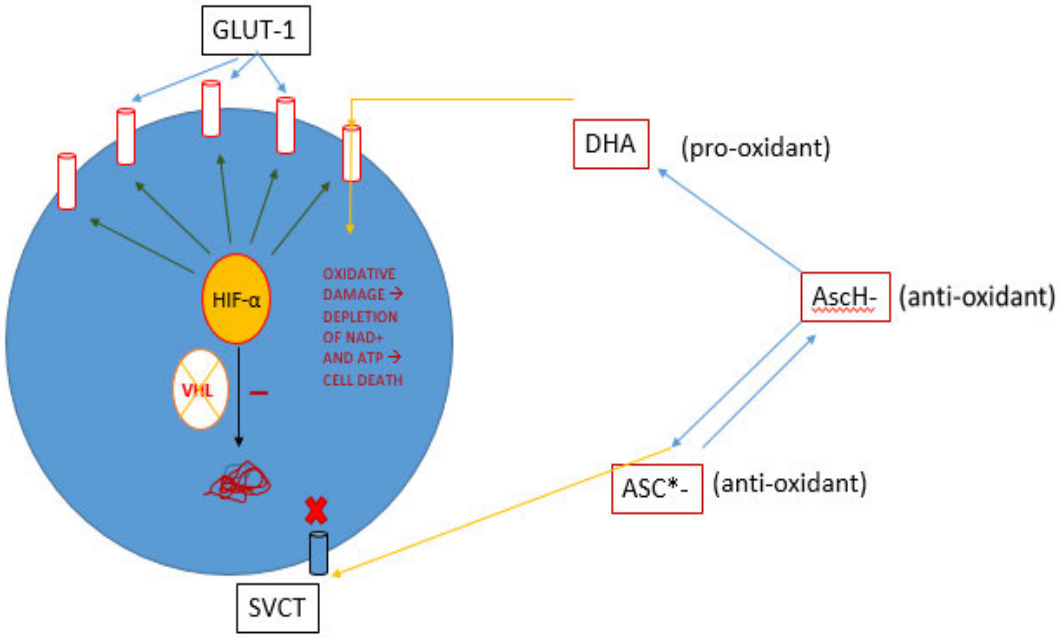


Fig 2. With loss of VHL activity in clear cell RCC, HIF-α avoids proteasomal degradation and is stabilized. HIF-α increases the expression of GLUT-1 (Glucose transporter-1) in an unregulated manner to increase uptake of glucose into the cell to meet increased metabolic demands via anaerobic glycolysis. Ascorbate (AscH-), being a water soluble antioxidant, can undergo two consecutive, one-electron oxidations resulting in the formation of ascorbate radical (Asc^{*-}) and dehydroascorbic acid (DHA); and the DHA (i.e oxidized Vitamin C) is taken up without regulation via the Glut 1 receptors, resulting in oxidative damage and depletion of ATP stores. The anti-oxidant form AscH-, is unable to enter the cell due to downregulation of Sodium dependent Vitamin C transporter (SVCT) with increasing intracellular vitamin C concentration. In the study Tian et al (ref 26), inhibition of HIF activity with shRNA resulted in reduced Vit C induced toxicity and inhibiton of Glut 1 also had the same effect, further supporting this mechanism.

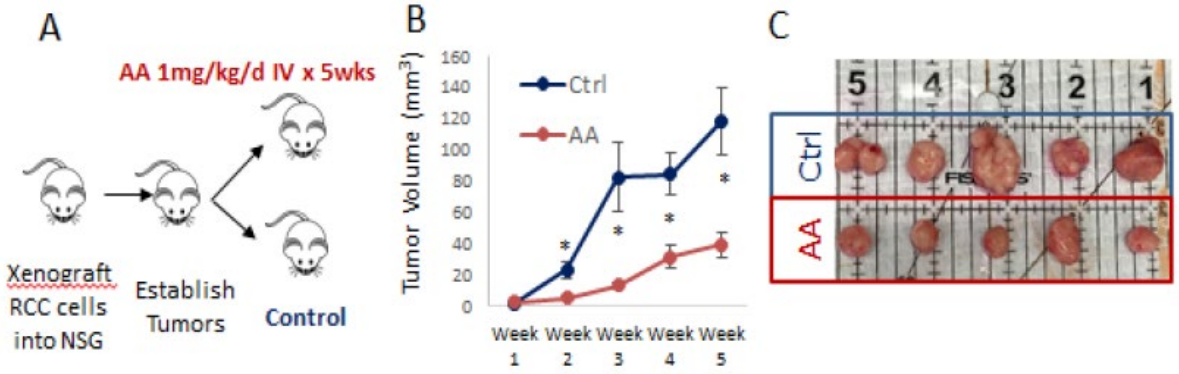
Considering that a majority of ll ccRCC are VHL mutant and as a result have high constitutive HIF activity, at least one of the two mechanisms elaborated above would be present in a large majority. In fact, there are case reports of remarkable benefit of high dose vitamin C therapy in renal cancer and bladder cancer, which are known to have dominant HIF pathway. Put together, these studies suggest that high dose vitamin C therapy may be more effective in cancers with a dominant HIF pathway.[27] Extensive clinical experiences with

Vitamin C in cancer have been documented mainly in the form of reports or series and even protocols for intravenous vitamin C in cancer have been suggested. [28-30] The fascinating phenomenon of intratumoral necrosis reported in some patients given high dose vitamin C may suggest that the hypoxic areas of tumors with high HIF activity may be particularly susceptible to high dose vit C. In VHL deficient ccRCC however, there is constitutive activation of HIF pathway and potentially high intracellular concentrations could be achieved throughout the tumor. TKIs (pazopanib/ sunitinib) that are the approved first line therapies in metastatic ccRCC, inhibit VEGF, thereby inhibiting neovascularization and theoretically causing more hypoxic area within the tumor with higher HIF activity, which could enhance the anticancer effect of Vitamin C.

1.3 Mechanism 3- Epigenetics

Clear cell RCC is known to have genome wide hypermethylation, and the degree of hypermethylation has been correlated with survival [31]. TET is an enzyme that converts methylcytosine to hydroxymethylcytosine, which then leads to demethylation. Preliminary data from our lab reveals loss of hydroxymethylation in high grade ccRCC patient samples, likely due to deficient TET activity (since TET is the only known enzyme responsible for conversion of methylcytosine to hydroxymethylcytosine). Vitamin C was shown to increase TET activity in embryonal stem cells in a Nature paper in 2013 [32] and we have shown that TET activity is increased with ascorbic acid in RCC cell lines 769P and 786-O. We further confirmed this by studying genome wide methylation and hydroxymethylation using mass spectrometry (LC/ESI-MS/MS) which revealed a decrease in total methylcytosine and increase in the fraction of hydroxymethylated DNA, correlating with the increase in TET activity. QPCR of Smad 7, a tumor suppressor gene of the TGF beta pathway known to be silenced by methylation was found to be upregulated with vit C. Proliferation assay data (MTT) revealed that the combination of pazopanib and vit C is better than either alone; and either alone is better than control. Xenograft data revealed a significant proliferation inhibition of ccRCC with single agent IV AA.

Ascorbic acid in vivo leads to inhibition of RCC tumor growth (unpublished):



A: RCC cells (786O) were xenografted into immunodeficient NSG mice. After tumors were established, treatment was initiated with IV AA (1mg/kg/d) or vehicle and tumor measurements were conducted (A). AA treatment led to significantly delayed tumor growth (B,C) (TTest, P<0.05, Means +/- S.E.M; N=10 in each cohort).

This background provides the rationale for exploring the effect of high dose ascorbic acid in VHL mutant clear cell RCC, exploiting the mechanisms of ascorbate induced toxicity i.e extracellular production of H2O2 within the tumor (potentially enhanced by the high iron content in the tumor micro-environment that has been demonstrated in ccRCC), intracellular accumulation of oxidized vitamin C (secondary to high HIF activity seen in ccRCC) and TET dependent demethylation of the hypermethylated genome causing re-expression of tumor suppressors.

High dose vitamin C is known to be well tolerated and to have negligible side effects in patients with preserved renal function [33, 34] and has been shown in many studies to improve the quality of life in advanced cancers.[35-37] Multiple phase I clinical trials of intravenous ascorbate in patients with advanced cancer measured plasma concentrations of ascorbate and evaluated clinical consequences. [33, 38, 39] In the study by Riordan and colleagues, patients were given continuous infusion of 0.15 to 0.7 g kg^{-1} day^{-1} for up to eight weeks; in the Hoffer study, ascorbate was administrated three times per week at fixed doses of 0.4, 0.6, 0.9 and 1.5 g kg^{-1}; and in the most recent study by Monti et al., patients received 50, 75 and 100 g per infusion (three infusions per week) for 8 weeks with concomitant IV gemcitabine and oral erlotinib. In the Riordan study, ascorbate concentrations in serum during therapy ranged from 0.28 to 3.8 mM. In the Hoffer study, peak plasma ascorbate concentrations ranged from 2.4 to 26 mM. When 1.5 g kg^{-1} was administered, plasma ascorbate concentrations exceeded 10 mM for ≈4.5 h, levels that have been shown to induce cell killing in a variety of cancer cells [40, 41]. Finally in the Monti study, patients that received 100 g of ascorbate achieved peak plasma concentrations between 25 and 32 mM. All three trials demonstrated that high-dose intravenous ascorbate was well tolerated in cancer patients with normal renal function; the combination of ascorbate infusion with standard of care chemotherapies did not increase toxicity.

Since high dose intravenous vitamin C has been studied in combination with TKI sorafenib in hepatocellular carcinoma [42] and shown to be safe, we think it would be reasonable to conduct a phase 2 study with the therapeutic dose established in the phase 1 studies.

1.4 Proposal Hypotheses:

1. Combining high dose IV ascorbic acid with pazopanib for the first line treatment of clear cell metastatic ccRCC will result in improved treatment failure-free rate at 9 months, median progression-free survival, objective response rate, tolerance and duration on therapy compared to pazopanib alone.

Exploratory Hypotheses:

2. Patients with ccRCC having higher iron content in the tumor micro-environment, as determined by iron staining using Prussian blue reaction, will have a better response to the combination of IV ascorbic acid and pazopanib than those with lower iron content.

3. Patients with ccRCC having higher Hypoxia Inducible Factor (HIF-1 and HIF-2) expression, as determined by immunohistochemistry (IHC) detection, will have a better response to the combination of ascorbic acid and pazopanib than those with lower expression.

4. Patients with ccRCC having higher 5-methylcytosine (5-mC) and lower 5-hydroxymethylcytosine (5-hmC) expression, as determined by IHC detection, will have a better response to the combination of ascorbic acid and pazopanib than those with lower expression.

1.5 Rationale for Study Design

Patients with advanced ccRCC on standard first-line therapy with pazopanib was chosen as the optimal setting in which to estimate the effects of IV Vitamin C. As summarized in the preceding sections, ccRCC has a hypermethylated epigenome and high iron content in the tumor microenvironment. These are the conditions under which pharmacologic doses of Vitamin C are hypothesized to have an anti-tumor effect. Pazopanib is well tolerated and results in clinically significant objective responses and prolonged time to progression. However, most patients suffer from some side effects that can be quantified and are occasionally dose limiting. More than half of all patients with ccRCC treated with pazopanib do not have an objective response, and complete responses are rare. Responding tumors eventually develop resistance, with median time to progression of 9 months. Improvements in these outcomes would be of great clinical significance for patients with ccRCC and would be an important proof of principle for the study of IV ascorbic acid in other tumor types.

Pazopanib was widely used in the first line setting when enrollment to this trial began. Data from subsequent randomized trials have demonstrated an overall survival advantage compared to first-line sunitinib for ipilimumab plus nivolumab in intermediate or poor-risk patients, and for pembrolizumab plus axitinib in all prognostic groups. The newer regimens have not been compared head-to-head with pazopanib, and pazopanib continues to be appropriate for selected patients. To meet our targeted enrollment, however, we have amended the study design to allow prior immunotherapy such as ipilimumab plus nivolumab, since its mechanism of antitumor effect is not known to overlap with pazopanib or ascorbic acid.

A randomized controlled trial design was chosen as the optimal way to detect improvement in clinical outcomes with IV Vitamin C. While a placebo-controlled trial would be ideal, we could not justify the cost and logistics of

giving iv placebo three times per week. For an open-label design, we considered pazopanib alone or pazopanib plus oral ascorbic acid. A three-arm trial would be ideal, but costly and would take a long time to complete. Since oral ascorbic acid has been extensively studied and is considered ineffective, we chose instead a randomized phase II trial design with two treatment arms: Pazopanib plus IV ascorbate or pazopanib alone.

We also considered giving IV Vitamin C 2 times/ week instead of 3, but chose a 3 times/ week regimen since it is considered to be the most optimal regimen and has been used more frequently in phase 1 studies, we decided to pursue that. If a twice a week regimen showed minimal benefit, the question would arise if giving it 3 times/ week would have been more efficacious.

2.0 Goals

2.1 Primary Objective:

To estimate and compare treatment failure-free rate at 40 weeks from randomization of patients with unresectable/metastatic clear cell Renal Cell Carcinoma (ccRCC) receiving one of the following regimens:

- Arm A: Pazopanib 800mg daily plus intravenous (IV) ascorbic acid 1g/kg 3 times/week.
- Arm B: Pazopanib 800mg daily

2.2 Secondary Objective:

2.21 To estimate and compare the overall survival (OS) in patients receiving pazopanib with or without IV ascorbic acid

2.22 To estimate and compare the progression-free survival (PFS) in patients receiving pazopanib with or without IV ascorbic acid

2.23 To estimate and compare the overall response rate (ORR) in patients receiving pazopanib with or without IV ascorbic acid

2.24 To estimate and compare the duration on pazopanib treatment in patients receiving pazopanib with or without IV ascorbic acid

2.25 To assess the adverse events (AE) profile and safety of each treatment arm using the CTCAE

2.3 Correlative Research

2.31 Correlation between 5mC, 5hmC and H3K27me3 expression (as determined by IHC), as well as MeDIP/hMeDIP seq, and response to combination of IV ascorbic acid and pazopanib.

2.32 Correlation between iron content in tumor microenvironment (as determined by Prussian blue staining) and response to combination of IV ascorbic acid and pazopanib.

2.33 Correlation between HIF-1α and HIF-2α expression (as determined by IHC) and response to combination of IV ascorbic acid and pazopanib.

2.34 Correlation between GLUT1 expression (as determined by IHC) and response to combination of IV ascorbic acid and pazopanib.

2.35 Correlation between PDL1 expression (as determined by IHC) and response to combination of IV ascorbic acid and pazopanib.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 18 years

3.12 Histological confirmation of clear cell renal cancer.

3.13 Documented metastatic or unresectable disease and at least one measurable lesion by RECIST criteria. NOTE: Nephrectomy or ablation of the primary tumor is allowed prior to enrollment.

3.14 No prior systemic therapy for clear cell renal cancer; or have progressed after immunotherapy such as ipilimumab plus nivolumab in the first line. Other immunotherapies (e.g. interleukin-2) or additional lines of immunotherapy may be allowed after discussion with the Principal Investigator.

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

3.16 The following laboratory values obtained ≤21 days prior to randomization:

- ANC ≥1500/mm^3
- PLT ≥100,000/mm^3
- Hgb ≥9.0 g/dL NOTE: Subjects may not have had a transfusion ≤7 days of randomization
- Total Bilirubin ≤1.5 x ULN.
  - **NOTE**: For bilirubin elevation 1 to 1.5x ULN, ALT above 1.5 x ULN (upper limit of normal) is not permitted.
  - **NOTE**: For bilirubin elevation 1 to 1.5x ULN, AST above 1.5 x ULN (upper limit of normal) is not permitted.
- Alanine amino transferase (ALT) <2.5 X ULN, with normal bilirubin. **NOTE**: Concomitant elevations in bilirubin and ALT above 1.5 x ULN (upper limit of normal) is not permitted.
- Aspartate aminotransferase (AST) <2.5 X ULN, with normal bilirubin. **NOTE**: Concomitant elevations in bilirubin and AST above 1.5 x ULN (upper limit of normal) is not permitted.

- Creatinine ≤ 1.5 mg/dl OR creatinine > 1.5 mg/dl, estimated creatinine clearance must be >= 55 mL/minute by CockcroftGault formula:

Cockcroft-Gault Equation:

Creatinine clearance for males = **(140 - age)(weight in kg)** / (72)(serum creatinine in mg/dL)

Creatinine clearance for females = **(140 - age)(weight in kg)(0.85)** / **(72)(serum creatinine in mg/dL)**

- INR and aPTT ≤ 1.5 × ULN. NOTE: This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

3.17 Individuals of non-childbearing potential, *or* individual of childbearing potential with negative serum pregnancy test ≤7 days prior to randomization and willing to practice total abstinence or use a highly effective method of contraception, as outlined in item "c" below:

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

NOTE: Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).
Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

b. Childbearing potential, including any individual who has had a negative serum pregnancy test, ≤7 days prior to randomization.

c. Agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:
   - Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the

dosing period, and for at least 21 days after the last dose of investigational product;
- Oral contraceptive, either combined or progestogen alone
- Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year;
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject;
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

3.18 Provide informed written consent.

3.19 Willing to provide archive tissue samples for correlative research purposes (See Sections 4.0, 6.0 and 17.0.)

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Individuals/or persons who are nursing ;
- Individual/or persons who are pregnant;
- Individuals/or persons of childbearing potential who are unwilling to employ adequate contraception.

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

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

3.24 Prior history of receiving pazopanib or any other tyrosine kinase inhibitor treatments for malignancy.

3.25 Uncontrolled intercurrent illness including, but not limited to:
- Chronic ongoing or active infection,
- Symptomatic anemia,
- Uncontrolled hypertension [defined as systolic blood pressure (SBP) of ≥160 mmHg or diastolic blood pressure (DBP) of ≥ 100mmHg],
- Symptomatic congestive heart failure as defined by the New York Heart Association (NYHA) (see Appendix III; does not exclude Class III CHF),
- unstable angina pectoris,
- cardiac arrhythmia,

- evidence of active bleeding or bleeding diathesis,
- psychiatric illness/social situations that would limit compliance with study requirements,
- any other serious uncontrolled medical disorders in the opinion of the investigator.

3.26 History of a major thromboembolic event ≤ 6 months prior to randomization, including cerebrovascular accident, transient ischemic attack (TIA), myocardial infarction, symptomatic pulmonary embolism (PE) or untreated deep venous thrombosis (DVT), or coronary artery bypass graft surgery. NOTE: Subjects with recent DVT or asymptomatic PE who have been treated with therapeutic anticoagulating agents for at least 6 weeks are eligible.

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

3.28 Other active malignancy ≤5 years prior to randomization. EXCEPTIONS: Nonmelanoma skin cancer or carcinoma-in-situ of the cervix, or cancers with low metastatic potential (e.g. Gleason score 6 prostate cancer) treated with curative therapy. NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

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

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

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

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

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

3.29e Treatment with any of the following anti-cancer therapies ≤ 14 days prior to randomization:

- radiation therapy
- surgery or tumor embolization
- chemotherapy, immunotherapy
- biologic therapy
- investigational therapy
- hormonal therapy

3.29f Prior autologous or allogeneic organ or tissue transplantation.

3.29g Elective or planned major surgery to be performed during the course of the trial.

3.29h Receiving any medications or substances that are strong or moderate inhibitors of CYP3A4 (for a listing of medications or substances see Appendix V) Use of strong or moderate inhibitors are prohibited ≤ 7 days prior to randomization.

3.29i Receiving any medications or substances that are inducers of CYP3A4 (for a listing of medications or substances see Appendix V). Use of inducers are prohibited ≤ 7 days prior to randomization.

3.29j Glucose-6-phosphate dehydrogenase (G6PD) deficiency (i.e. below normal limits).

3.29k End-stage renal disease (estimated GFR <55 ml/min/BSA), unless the estimated creatinine clearance by Cockcroft Gault is ≥55 ml/min prior to randomization.

3.29l History of calcium oxalate stones.

3.29m History of iron overload.

3.29n Unable to swallow oral medications.

3.29o History of myocardial infarction ≤6 months, current symptomatic CHF or LVEF <40% or > grade 2 diastolic dysfunction, with no symptoms or signs of heart failure.

4.0 Test Schedule

Cycle length = 28 days.

Tests and procedures	Active Monitoring Cycle length = 28 days +/- 7 day window for study visits and tests.[5]				
	≤21 days prior to randomization	Prior to each new cycle (≤7 days)	Prior to 3rd and subsequent odd cycles (5, 7, 9, etc.)	At PD, withdrawal, removal, or end of protocol treatment	Observation (Clinical follow-up)
Informed Consent	X				
History and exam, wt., ECOG PS	X	X		X	X
Height	X				
Adverse event assessment	X	X[6]		X	X
Echocardiogram (2D M-Mode)	X[8]				
Hematology: CBC/ differential	X	X[5]		X	X
Chemistry: SGOT (AST), alk phos, T. bili, creatinine, calcium, phos, glucose, Na, K, ALT, GFR, LDH[11]	X	X[4,5]		X	X
G6PD test	X[R, 9]				
Urinalysis	X			X	
Thyroid function test (TSH)	X		X		
Coagulation test: INR, APTT	X				
Tumor measurement	X[1]		X[1]		X[1, 10]
CT/MRI brain, if needed (See Section 3.29a)	X		X		
Bone scan[12]	X		X		
ECG	X		X		
Pregnancy test (serum)	X[2]				
Mandatory archival tissue collection (see Section 17.2)	X[R, 7]				
Patient Medication Diary (Appendix II)		X[3]		X[3]	

[1] CT chest, abdomen, and pelvis with IV contrast. If unable to receive IV contrast, MRI abdomen/pelvis with contrast and CT chest without contrast are acceptable. Use same imaging method throughout the study.

[2] For individuals of childbearing potential only. Must be done ≤ 7 days prior to randomization.

[3] The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution every 4 weeks.

[4] For ARM- A (ascorbic acid group) only: Draw at baseline then weekly for Cycle 1, then for subsequent cycles on Day 14 and Day 28. For ARM B only: draw at baseline then once every cycle.

[5] Labs do not have to be repeated prior to Cycle 1 if they were done ≤ 5 days prior to cycle.

[6] Starting with Cycle 2, AE's for Cycle 1 are assessed prior to the beginning of Cycle 2 and are recorded under Cycle 1 AE, following this format for all subsequent cycles.

[7] Receipt of archival tumor tissue (if available) is not required for study randomization and initiation of therapy. . However, it is mandatory to receive the required tissue ≤ 30 days from registration.

[8] Echocardiogram done ≤ 6 months prior to randomization is acceptable.

[9] G6PD = Glucose-6-phosphate dehydrogenase. If G6PD is found to be below normal limits, patient will be ineligible for the trial. If below normal limits, the test can be repeated up to two additional times. One normal result is sufficient for eligibility if done within 6 months prior to randomization (does not need to be repeated within the 21-day window).

[10] Imaging frequency is every 8 weeks or as clinically indicated, until progression or 2 years since study randomization, whichever is first, or per treating physician discretion.

[11] LDH = Lactate dehydrogenase. Include with chemistries at baseline and during treatment.

[12] For patients with a history of bone metastases or for whom there is clinical suspicion of bone metastases at study entry.

[13] If the urinalysis prior to randomization indicates proteinuria, urine protein/ Cr or 24hr urine protein would need to be monitored as clinically indicated throughout the study period. Pazopanib dose modification based on significant proteinuria to be followed, as stated in section 8.12.

[R] Research funded (see Section 19.0).

5.0 Stratification Factors:

- MSKCC risk category (Favorable risk vs. Intermediate risk vs. Poor risk. See Appendix VI for MSKCC risk score.)

- Sarcomatoid differentiation (Yes vs. No)

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] go to Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the above web page under Study Resources section, "Application Training".

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted]. Click on "Registration, Installation & Entry Instructions".

6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19 and 17.2).

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using online ACCRU Regulatory Management Systems (ARMS) If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.14 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.15 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her tissue sample(s) to outside researchers.

6.16 Treatment cannot begin prior to randomization and must begin ≤ 14 days after randomization.

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

6.18 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.19a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.19b Study drug is available on site.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon ref – see below). The goal of the algorithm is to maintain arm balance with respect to the stratification factors (see Section 5.0).

In order to ensure that treatment assignment is not deterministic, a level of randomness has been added to the algorithm such that patients will be assigned to the arm that leads to less imbalance 90% of the time.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention per institutional guidelines.

Arm	Agent	Dose Level	Route	Frequency	ReRx[1]
A	Pazopanib	800mg	PO	Once Daily	Every 28 days
	Ascorbic acid	1g/kg, titrate first 3 doses: 0.25, 0.5, and 0.75g/kg) in 1000ml sterile water** The maximum allowed dose is 100g.	IV (0.75-1g/min IV*)	3 times/ week (Mon/Wed/Fri) or (Tue/Thu/Sat) or	
B	Pazopanib	800mg	PO	Once Daily	

1. Cycles = 28 days

* Start infusion rate at 0.75g/minute. If no dizziness after 15 minutes the rate can be increased to 1 g/min. Infusion times are approximate (+/- 15 minutes) and may need to be adjusted based on patient tolerability.

**Exceptions during titration: First dose in 250 ml sterile water. Second dose in 500ml sterile water. If the maximum dose (based on the patient's weight) is less than 75 grams, then dose schedule is 25g, 50g, and then maximum calculated dose.

NOTE: Patients should be observed for 30 minutes after administration of ascorbic acid for at least the first 5 doses. Ascorbic acid infusions may not be given less than 24 hours apart. If patients miss one day of ascorbic acid IV, they can continue the following day. **If a patient misses more than 4 doses of ascorbic acid IV in any cycle, the local study doctor must consult with the Principal Investigator before the patient will be allowed to continue on study.**

7.2 Protocol treatment for Arm A consists of four 200mg tablets (800 mg) of pazopanib by mouth once each day plus IV ascorbic acid at 1g/kg given 3 times/week.

Protocol treatment for Arm B consists of four 200mg tablets (800 mg) of pazopanib by mouth once each day.

7.21 Dosage and Administration of Pazopanib

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

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

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

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

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

If a subject's treatment with pazopanib has been interrupted for more than 21 consecutive days, the local medicals doctor must contact the Study Principal Investigator to review the subject's condition in order to resume the treatment.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 28 days during treatment

7.5 Administration of IV ascorbic acid by a non-study local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

8.1 Pazopanib

8.11 Pazopanib Dose Reduction Levels

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

8.12 Dose Modifications for Pazopanib at Time of Treatment

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT			
Investigations	Platelet count decreased Grade 3 or 4	Pazopanib	Omit until ≤ Grade 2 then restart at next lower dose level. If no recovery to grade 2, discontinue
Investigations	Prolongation of QTc Interval (If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually read ECGs.		
	QTc ≥ 480 < 500 msec	Pazopanib	Continue pazopanib; monitor as clinically indicated. Consider reducing Pazopanib dose to dose level 1 and gradually increase as tolerated. Recommend discontinuing any other QT prolonging agent in the patient's medication list.
	QTc ≥ 500 msec		Interrupt Pazopanib and discontinue any other QT prolonging agent in the patient's medication list. Recheck EKG in 1 week, If < 500msec, restart Pazopanib at dose level 2 with close monitoring. If recurrent/ refractory QTc > 500msec, discontinue pazopanib and continue follow-up per protocol.
Renal and urinary disorders	Creatinine ≥Grade 3	Pazopanib	Omit until < Grade 3 then restart at next lower dose level. If ≥ Grade 3 recurs, reduce one dose level again until no dose can be given (see Section 8.2 regarding ascorbic acid dose reduction)

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Proteinuria UPC <3 UPC ≥3 or 24-h urine protein ≥3g	Pazopanib	Continue pazopanib at the current dose; monitor as clinically indicated 1. Interrupt pazopanib. 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. 3. If UPC ≥3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2. 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, **discontinue pazopanib** and continue follow-up per protocol.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Vascular disorders	Thromboembolic event DVT/PE Grade 2	Pazopanib	Continue pazopanib at the current dose; monitor as clinically indicated
	Grade 3		Omit and initiate anticoagulant. Restart at reduced dose if • Subject must have been treated at desired level of anticoagulation for at least 1 week • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Note: When treating with warfarin, INR S/B monitored within 3 to 5 days after any change in pazopanib dosing and then at least weekly until INR is stable. The dose of warfarin may need to be adjusted to maintain the desired level of anticoagulation.
	Grade 4 Arterial Thrombosis/Ischemia Any Grade		**Discontinue pazopanib** **Discontinue pazopanib**
	Thrombocytopenia: Investigate and document underlying cause Grade 1 or 2 Grade 3 or 4		Continue pazopanib with current dose; monitor as clinically indicated. Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 2. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue Pazopanib and follow-up per protocol.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Vascular disorders	Hypertension (Scenario A) Asymptomatic and persistent[d] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, Or Clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Pazopanib	• Continue pazopanib treatment at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
	(Scenario B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, Or Failure to achieve well-controlled BP within 2 weeks in Scenario A	Pazopanib	• Interrupt pazopanib treatment if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled[e], restart pazopanib treatment reduced by one dose level

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Symptomatic[f] hypertension or Persistent[g] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	Pazopanib	• Interrupt pazopanib treatment • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP • Referral to a specialist for further evaluation and follow-up is recommended Once BP is well controlled, restart pazopanib treatment **reduced by one dose level**
	Refractory hypertension unresponsive to above interventions.	Pazopanib	• **Permanently discontinue pazopanib** treatment • Continue follow-up per protocol.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Cardiac Disorders	LVEF-drop (%) or CTCAE grade Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN Or LVEF drop >15% from baseline regardless of whether value is below institution's LLN.	Pazopanib	• Interrupt pazopanib study treatment and repeat ECHO within 2 weeks[b] and monitor and control BP. • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline) -Restart study treatment[f] reduced by one dose level *(Contact ACCRU if there are any questions prior to restarting)* -Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; monitor BP; continue in intervals of 12 weeks thereafter • If repeat LVEF does not recover within 4 weeks -Consult with cardiologist -**Permanently discontinue pazopanib** treatment Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution. *(Contact ACCRU if there are any questions)*
	Symptomatic[c:] Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Symptomatic[c] Grade 4: resting LVEF <20%	Pazopanib	• **Permanently discontinue pazopanib** treatment • Consult with cardiologist • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Gastrointestinal disorders	GI bleed Grade 2 Grade 3 or Grade 4	Pazopanib	Interrupt pazopanib, restart at dose level 2 when bleeding has resolved and gradually titrate up as tolerated. **Discontinue Pazopanib**
Respiratory, thoracic and mediastinal disorders	Pulmonary bleed Grade 1	Pazopanib	For Grade I hemoptysis, continue pazopanib at the current dose; monitor as clinically indicated.
	Grade 2		Interrupt pazopanib, restart at dose level 2 when bleeding has resolved and gradually titrate up as tolerated.
	Grade 3 or 4 or Recurrent ≥ Grade 2 event after dose interruption/reduction.		**Discontinue pazopanib** and continue with follow-up per protocol.
Dermatology/ Skin	Dermatitis Grade 2 skin changes w/pain, limiting ADL's Grade3 severe skin changes w/pain Limiting self-care ADL's	Pazopanib	Omit until ≤ Grade 1, then restart at next lower dose level. If recurrent, reduce by another dose level or discontinue **Discontinue pazopanib**

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Skin and subcutaneous tissue disorders	Palmar-plantar Erythrodysesthesia Syndrome Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis) Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis) Grade 3 Severe skin changes with pain and limiting self-care	Pazopanib	Continue pazopanib at present dose 1. Hold pazopanib 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart pazopanib with a dose reduction to dose level -1 (if it was a full dose [800mg]) or one dose lower than the patient was receiving prior to developing the skin changes. 4. If recurrent consider a further dose reduction by 1 dose level until dose level -2. If patient has a Grade 2 toxicity on dose level -2, then consider stopping the drug. **Discontinue pazopanib**
Blood and lymphatic system disorders	Anemia	Pazopanib	No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.
All Other	Grade 1 Grade 2 or 3, if clinically significant Grade 4	Pazopanib	Continue pazopanib; monitor as clinically indicated. Omit until ≤ Grade 1 Restart pazopanib dose-reduced by 200 mg (1 dose level) and monitor as clinically indicated. **Discontinue Pazopanib** and continue follow-up per protocol.

* Located at [redacted]

** Use the following to describe actions in the Action column:
- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

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

8.13 Dose Modifications for Pazopanib at Time of Retreatment

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

→→ *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ←←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Vascular disorders	Thromboembolic event DVT/PE Grade 3 Grade 4 Arterial Thrombosis/Ischemia Any Grade	Pazopanib	Hold and initiate anticoagulant. Decrease 1 dose level if • Subject must have been treated at desired level of anticoagulation for at least 1 week • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Note: When treating with warfarin, INR S/B monitored within 3 to 5 days after any change in pazopanib dosing and then at least weekly until INR is stable. The dose of warfarin may need to be adjusted to maintain the desired level of anticoagulation. **Discontinue pazopanib** **Discontinue pazopanib**
Vascular disorders	Hypertension	Pazopanib	See table 8.3
Gastrointestinal disorders	GI bleed Grade 2 Grade 3 or 4	Pazopanib	Interrupt pazopanib, restart at dose level 2 when bleeding has resolved and gradually titrate up as tolerated. **Discontinue Pazopanib**
Respiratory, thoracic and mediastinal disorders	Pulmonary bleed Grade 2 Grade 3 or 4	Pazopanib	Interrupt pazopanib, restart at dose level 2 when bleeding has resolved and gradually titrate up as tolerated. **Discontinue Pazopanib**

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Dermatology/ Skin	Dermatitis Grade 2 skin changes w/pain, limiting ADL's Grade3 severe skin changes w/pain Limiting self-care ADL's	Pazopanib	Hold until ≤ 1, then restart at next lower dose level. If recurrent, reduce by another dose level or discontinue. **Discontinue pazopanib**
All others	Grade 2 or 3, if clinically significant Grade 4		Hold until ≤ Grade 1 **Discontinue pazopanib**

* Located at [redacted]

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

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

8.14 Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[c] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[0] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria[c]:** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. **Recurrence – Liver Event Stopping Criteria[c]:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[0] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria[c]:** (1) Discontinue pazopanib immediately. (2) Perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging -Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.

Event	Dose Modification Algorithms
For isolated total bilirubin[0] elevation without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. (2) If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.

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

8.2 Dose Modifications for IV Ascorbic Acid at Time of Treatment

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
DAY OF TREATMENT ADVERSE EVENT			
Renal and Urinary disorders	Renal Function	Ascorbic Acid	**SEE TABLE IMMEDIATELY BELOW(section 8.21)**
General Disorders and Administration Site Conditions	Dizziness during Infusion Grade 1 (mild) -3 (severe) Grade 1 = mild unsteadiness or sensation of movement Grade 2 = Moderate unsteadiness or sensation of movement limiting instrumental ADL Grade 3 Severe	Ascorbic Acid	Stop infusion until dizziness resolves (about 10-15 min), restart at half the infusion rate when dizziness has resolved, and gradually increase as tolerated. If dizziness re-occurs then repeat above instructions.
Respiratory, Thoracic and Mediastinal Disorders	Bronchopulmonary hemorrhage Grade 1 Grade 2-4	Ascorbic Acid	 No dose adjustment required Hold until resolution to grade 1
Vascular Disorders	→Hypotension Grade 2 Grade 3 Grade 4 →Hemorrhage (any organ) Grade 1 Grade 2-4	Ascorbic Acid	 No dosage adjustment required Cut dose by 50% Hold until improvement to Grade 3 No dose adjustment required Hold until resolution to grade 1
Gastrointestinal Disorders	→Gastrointestinal symptoms (Nausea, vomiting, or diarrhea) Grade 2-3 Grade 4	Ascorbic Acid	Antiemetics and antidiarrheals can be used and should be used prior to reducing dose. If they are ineffective then reduce dose by 50%. Provision to gradually increase (at next infusion day) back to target dose as tolerated at treating physician judgment Hold until resolution to grade 3 or below

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Hepatobiliary Disorders	→Hepatobiliary disorders Other, specify Grade 2-3 Grade 4	Ascorbic acid	 No dose adjustment necessary Cut dose by 50%

* Located at [redacted]
** Use the following to describe actions in the Action column:
- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.21 Dose modifications for IV Ascorbic Acid based on Renal function

Increase from baseline serum creatinine	**Creatinine < 2.0 mg/dL**	**Creatinine ≥ 2.0 mg/dL**
< 50%	• Continue treatment. • No dose reduction.	• Hold dose. • Ensure adequate hydration. • Resume when creatinine < 2.0 mg/dL.
50% (1.5 times)	• Ensure adequate hydration. • For first occurrence only: ○ Administer 50% of the previous dose. ○ Increase the next scheduled dose to 75%, then to 100% as long as creatinine remains < 2 times baseline. ○ Continue at the highest dose tolerated.	
60% (1.6 times)		
70% (1.7 times)		
80% (1.8 times)		
90% (1.9 times)		
≥ 100% (≥2 times)	• Hold dose. • Ensure adequate hydration. • Resume when creatinine < 2 times baseline.	• Hold dose. • Ensure adequate hydration. • Resume when creatinine < 2.0 mg/dL and < 2 times baseline.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's may be used at the discretion of the attending physician.

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

9.3 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

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

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

9.4 Dizziness during infusion: Stop infusion until dizziness resolves (about 10-15 min), restart at half the infusion rate when dizziness has resolved, and gradually increase as tolerated. If dizziness re-occurs then repeat above instructions.

10.0 Adverse Event (AE) Reporting and Monitoring

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

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

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

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

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

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

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

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

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AE's are reported in the package insert or the literature, including AE's resulting from a drug overdose.

2. Follow site-specific reporting guidelines.

3. Submit MedWatch form 3500A [redacted] or found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU web site) to the ACCRU SAE Coordinator via fax [redacted]

4. The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the

investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.53 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v4.0 grading. If CTCAE v4.0 grading is not used, note the grading scale used in the table below

System Organ Class (SOC)	**Adverse event/Symptoms**	**Baseline**	**Each evaluation**
General Disorders	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Diarrhea	# of stools	X
	Mucositis oral	X	X
Injury, poisoning and procedural complications	Vascular access complication		X
Infections and infestations	Catheter related infection		X
Investigations	Blood bilirubin increased	X	X
	Aspartate aminotransferase increased	X	X
	Alanine aminotransferase increased	X	X
	Creatinine increased	X	X

10.54 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU) Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable)

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

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

10.543 Grade 5 AEs (Deaths)

10.5431 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5432 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.55 Refer to the instructions in the Case Report Forms (CRF) Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST Guideline

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

Response and progression will be evaluated in this study using the most recent criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). [43] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

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

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

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

11.22 Non-Measurable Disease

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

Note: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).

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

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

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

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

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

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

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

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

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

11.42 Non-Target Lesions & Non-Target Lymph Nodes

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

11.43 Response Criteria

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

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

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

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

- Complete Response (CR): All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- Progression (PD): At least one of the following must be true:

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

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

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

11.44 Overall Objective Status

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

For Patients with Measurable Disease

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

*See Section 11.431
** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

12.0 Descriptive Factors

- Nephrectomy (Yes vs. No)

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol up to a maximum of 10 cycles or until PD whichever is first. After 10 cycles of treatment, treatment may be continued off study per physician discretion. Patients who are CR, PR, or SD after 10 cycles will move to Observation Phase of the trial (see section 13.2).

13.2 Observation:

Patients who complete protocol treatment, or discontinue protocol treatment due to unacceptable toxicity or other complicating disease, will be followed every 8 weeks (+/- 7 days) for a maximum of 2 years from the registration in the Observation Phase per Section 4.0 of the protocol.

13.3 Event Monitoring:

Patients who develop PD, choose alternative therapy, refuse treatment or refuse to be followed in observation at any time will go to the Event Monitoring phase and be followed every 6 months (+/- 30 days) for a maximum of 3 years from registration per Section 18.0 of the protocol.
Treatment options for these patients are at the discretion of the treating physician.

13.4 Patients who develop PD in the CNS only should receive whole brain radiotherapy (WBRT) and continue treatment on study after completion of WBRT.

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

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

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

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens: None

15.0 Drug Information

The study drug is IND exempt because:

• The drug product is lawfully marketed in the United States.
• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
• In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
• The investigation is conducted in compliance with the requirements of §312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

15.1 **Pazopanib (Votrient®)**

15.11 **Background:** Tyrosine kinase (multikinase) inhibitor; limits tumor growth via inhibition of angiogenesis by inhibiting cell surface vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor receptors (PDGFR-alpha and -beta), fibroblast growth factor receptor (FGFR-1 and -3), cytokine receptor (cKIT), interleukin-2 receptor inducible T-cell kinase, lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms)

15.12 **Formulation**: Commercially available for oral administration as 200 mg tablets.

15.13 **Preparation and storage**: Refer to package insert for complete dispensing instructions. Store tablets at room temperature between 20ºC and 25ºC (68ºF and 77ºF); excursions permitted between 15ºC and 30ºC (59ºF and 86ºF).

15.14 **Administration:** Refer to the treatment section for specific administration instructions. The manufacturer recommends pazopanib be administered on an empty stomach, 1 hour before or 2 hours after a meal. Do not crush tablet (rate of absorption may be increased; may affect systemic exposure).

15.15 **Pharmacokinetic information**:
Absorption and Bioavailability: Pazopanib is absorbed orally with median time to achieve peak concentration of 2 to 4 hours after the dose. Median absolute bioavailability is 21%. Systemic exposure to pazopanib is increased when administered with food. Administration with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Pazopanib should be administered at least one hour before or 2 hours after a meal.
Plasma protein binding: 99%
Half-life elimination: 30.9 hours after administration of a single 800 mg dose
Time to peak, plasma: 2-4 hours
Excretion: Primarily via feces with renal elimination accounting for < 4% of the administered dose
Metabolism: In vitro studies demonstrate pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

15.16 **Potential Drug Interactions**:
Cytochrome P450 Effect: Pazopanib is metabolized principally by CYP3A4 with minor contributions from CYP1A2 and CYP3A4. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4 Inhibitors and Inducers: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Pazopanib should not be used if chronic use of strong CYP3A4 inducers cannot be avoided.

Transporter Inhibitors: In vitro studies suggested that pazopanib is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influence by products that affect P-glycoprotein and BCRP. Concomitant treatment with strong inhibitors of P-glycoprotein and BCRP should be avoided.

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

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

Concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor, decreased the exposure of pazopanib by approximately 40% (AUC and Cmax). Concomitant use of pazopanib with drugs that raise gastric pH should be avoided. If such drugs are needed, short acting antacids should be considered in place of proton pump inhibitors and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure.

Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range should be performed.

15.17 **Known potential toxicities**:
Consult the package insert for the most current and complete information. **Important Safety Information including Boxed WARNING: Severe and fatal hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, has been observed in clinical trials. Monitor hepatic function and interrupt, reduce or discontinue dosing as recommended.**

Common known potential toxicities, > 10%:
Cardiovascular: Hypertension, bradycardia, peripheral edema, cardiac insufficiency
Central nervous system: Fatigue, headache, dizziness
Dermatologic: Hair discoloration, exfoliative dermatitis, alopecia, dermatological disease,

hypopigmentation, palmar-plantar erythrodysesthesia
Endocrine & metabolic: Weight loss, hyperglycemia, increased thyroid-stimulating hormone (TSH), decreased serum albumin, hypophosphatemia, hyponatremia, hypomagnesemia, hypoglycemia, hyperkalemia
Gastrointestinal: Diarrhea, nausea, decreased appetite, anorexia, vomiting, dysgeusia, increased serum lipase, gastrointestinal pain, abdominal pain, mucositis, stomatitis
Hematologic & oncologic: Leukopenia, lymphocytopenia, thrombocytopenia, neutropenia, hemorrhage

Hepatic: Increased serum AST, increased serum ALT, increased serum bilirubin, decreased serum albumin, increased serum alkaline phosphatase
Neuromuscular & skeletal: Musculoskeletal pain, myalgia, weakness
Respiratory: Dyspnea, cough
Miscellaneous: Tumor pain

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Chest pain, left ventricular systolic dysfunction, venous thrombosis, ischemia, myocardial infarction, prolonged QT interval on ECG, facial edema, transient ischemic attacks
Central nervous system: Insomnia, voice disorder, chills
Dermatologic: Skin rash, skin depigmentation, xeroderma, nail disease
Endocrine & metabolic: Hypothyroidism
Gastrointestinal: Dyspepsia, anal hemorrhage, gastrointestinal fistula, gastrointestinal perforation
Hematologic & oncologic: Oral hemorrhage, rectal hemorrhage
Ophthalmic: Blurred vision
Renal: Proteinuria, hematuria
Respiratory: Epistaxis, pneumothorax, hemoptysis

Frequently not defined:
Cardiovascular: Decreased left ventricular ejection fraction, hypertensive crisis
Central nervous system: Reversible posterior leukoencephalopathy syndrome
Hematologic & oncologic: Hemolytic-uremic syndrome, neutropenic infection, thrombotic thrombocytopenic purpura
Hepatic: Hepatotoxicity, sever hepatotoxicity
Infection: Serious infection
Neuromuscular & skeletal: Arthralgia, muscle spasm

Rare, less than 1% (limited to important or life-threatening):
Cardiac disease, cerebral hemorrhage, cerebrovascular accident, congestive heart failure, interstitial pneumonitis, nephrotic syndrome, pancreatitis, retinal changes (tear), retinal detachment, torsade de pointes

15.18 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 **Nursing Guidelines:**

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

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

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

15.194 Inform patient of possible changes in hair color.

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

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

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

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

15.199aCardiac side effects (CHF, MI, chest pain, etc). While rare can be serious and life threatening. Instruct patient to report any cardiac symptoms to study team immediately.

15.199bRPLS, CVA, and TIA are uncommon, but are life threatening. Instruct patient to report any neurological symptoms to the study team immediately.

15.2 **Ascorbic Acid (Vitamin C, ASCOR®)**

15.21 **Background:** Ascorbic acid (vitamin C), a water-soluble vitamin, is an essential coenzyme for collagen formation, tissue repair and synthesis of lipids and proteins. It acts both as a reducing agent and as an antioxidant and is necessary for many physiologic functions such as metabolism of iron and folic acid, resistance to infection, and preservation of blood vessel integrity.

15.22 **Formulation**: ASCOR® (ascorbic acid injection) 25,000 mg/50 mL (500 mg/mL) for intravenous use is a colorless to pale yellow, preservative-free, hypertonic, sterile, non-pyrogenic solution of ascorbic acid. [49] ASCOR must be diluted with an appropriate infusion solution (e.g. 5% Dextrose Injection, USP, Sterile Water for Injection, USP). Each ASCOR, 50 mL, Pharmacy Bulk Package vial contains 25,000 mg ascorbic acid, equivalent to 28,125 mg sodium ascorbate. Each mL of ASCOR contains 500 mg of ascorbic acid (equivalent to 562.5 mg of sodium ascorbate which amounts to 65 mg sodium/mL of ASCOR), 0.25 mg of edetate disodium, and water for injection. Sodium hydroxide and sodium bicarbonate are added for pH adjustment (pH range 5.6 to 6.6). It contains no bacteriostatic or antimicrobial agent.

15.23 **Preparation and storage**:

Penetrate each PBP vial closure **only one time** with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents. Given that pressure may develop within the vial during storage, exercise caution when withdrawing contents from the vial. Once the closure system has been penetrated, **complete all dispensing from the PBP vial within 4 hours**. Each dose **must be used immediately**. Discard unused portion.

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect vials from light and product has an expiration of 24 hours at room temperature. This product contains no preservative.

15.24 **Administration:** Do not administer ASCOR as an undiluted intravenous injection. Administer 750mg – 1000 mg/minute as outlined in Section 7.1.
Start infusion rate at 0.75g/minute. If no dizziness after 15 minutes the rate can be increased to 1 g/min. Infusion times are approx. (±15 minutes) and may need to be adjusted based on patient tolerability. The maximum allowed dose is 100 g per infusion.

15.25 **Pharmacokinetic information:**

Distribution: Ascorbic acid is distributed widely in the body, with large concentrations found in the liver, leukocytes, platelets, glandular tissues, and lens of the eye. Based on data from oral exposure, ascorbic acid is known to be distributed into breast milk and crosses the placental barrier.
Metabolism: A major route of metabolism of ascorbic acid involves its conversion to urinary oxalate, presumably through intermediate formation of its oxidized product, hehydroascorbic acid.
Elimination: When the body is saturated with ascorbic acid, the plasma concentration will be about the same as that of the renal threshold; if further amounts are then administered, most of it is excreted in the urine. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion. The mean±SD (N=3) half-life observed in the single dose PK study as described above, was 7.4±1.4 h.
Excretion:
There is a renal threshold for ascorbic acid (Vitamin C); the vitamin is excreted by the kidney in large amounts only when the plasma concentration exceeds this threshold, which is approximately 1.4 mg/100 mL.

15.26 **Potential Drug Interactions:**

Antibiotics: Ascorbic acid may decrease activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Bleomycin is inactivated in vitro by ascorbic acid. If the antibiotic efficacy is suspected to be decreased by concomitant administration of ASCOR, discontinue ASCOR administration.

Amphetamine & Other Drugs Affected by Urine Acidification: Ascorbic acid may acidify the urine and lower serum concentrations of amphetamine by increasing renal excretion (as reflected by changes in amphetamine urine recovery rates). In case of decreased amphetamine efficacy discontinue ASCOR administration. Standard monitoring of therapy is warranted.
In addition, acidification of urine by ascorbic acid will alter the excretion of certain drugs affected by the pH of the urine (e.g. fluphenazine) when administered concurrently. It has been reported that concurrent administration of ascorbic acid and fluphenazine has resulted in decreased fluphenazine plasma concentrations. Standard monitoring of therapy is warranted.

Warfarin: Limited case reports have suggested interference of ascorbic acid with the anticoagulation effects of warfarin, however, patients on warfarin therapy treated with ascorbic acid doses up to 1000 mg/day (5 times the largest recommended single dose) for 2 weeks (twice the maximum recommended duration), no effect was observed. Standard monitoring for anti-coagulation therapy should continue during ascorbic acid treatment, as per standard of care.

Laboratory Test Interference: Because ascorbic acid is a strong reducing agent, it can interfere with numerous laboratory tests based on oxidation-reduction reactions (e.g. glucose, nitrite and bilirubin levels, leukocyte count, etc.). Chemical detecting methods based on colorimetric reactions are generally those tests affected. Ascorbic acid may lead to inaccurate results (false negatives) obtained for checking blood or urinary glucose levels, nitrite, bilirubin, and leukocytes if tested during or within 24 hours after infusion.

15.27 **Known potential toxicities**:
Most common adverse reactions are pain and swelling at the site of infusion.
Patients with glucose-6-phosphate dehydrogenase deficiency are at risk of severe hemolysis; a reduced dose is recommended.
Hot flashes, headache, fatigue, insomnia, stomach cramp, nausea and vomiting.
Allergy to ascorbic acid is extremely rare. Four cases of respiratory and cutaneous allergies to ascorbic acid have been documented.
Too rapid intravenous injection can cause temporary dizziness or faintness.
Acidification of urine by large doses of ascorbic acid might cause precipitation of urate, oxalate or cystine stones or drugs in the urinary tract, especially since some ascorbate is metabolized to oxalate. Some patients with pre-existing renal disease have been reported to develop renal failure following treatment with high doses of ascorbic acid.
High dosage of ascorbic acid may cause diarrhea.
Deep-vein thrombosis has been reported after large doses of ascorbic acid.
Rarely, decreased blood pH leading to sickle-cell crisis has been reported in patients with sickle cell disease.
At doses of greater than 600 mg, ascorbic acid has been reported to have a diuretic action.
High doses can increase serum cholesterol in atherosclerotic patients.

15.28 **Drug procurement:**

The ascorbic acid will be purchased from McGuff Pharmaceuticals and supplied to Clinic Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinic Research Services, a division of Rx Crossroads by McKesson.

Fax the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of ascorbic acid and will use the appropriate Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 **Nursing Guidelines:**

15.291 There are several possible drug- to drug interactions. Assess patient's concomitant medications including OTC and herbal products and cross-reference with section 15.16 in the protocol to assess for interactions.

15.292 Patients may experience hot flushes.

15.293 Headache is a possibility. Treat symptomatically and monitor for effectiveness.

15.294 If given IV, give over at least 15 minutes. Too rapid of infusion can cause dizziness and feeling faint. Some patients may need to have infusion slowed based on tolerability.

15.295 Rarely in patients who have a history of sickle-cell disease, patients could experience sickle cell crisis.

15.296 Patients who have renal impairment may be at higher risk of renal failure with higher doses. Monitor renal function closely and inform study team of any increases in creatinine. Additionally patients may be at higher risk of stones. Patients with a history of renal stones/calculi should be monitored closely.

15.297 Higher doses have been associated increases in serum cholesterol. Patients who have a history of hyperlipidemia may require additional monitoring as needed.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a randomized Phase II study which assess the efficacy of IV ascorbic acid in combination with Pazopanib (Arm A) when compared to Pazopanib alone (Arm B) in patients with metastatic/unresectable clear cell Renal Cell Carcinoma (ccRCC). Patients will be randomized at the time of registration at 1:1 ratio to either arm using a dynamic allocation procedure which balances the marginal distributions of the stratification factors (see Section 5) between the treatment regimens.

16.11 Primary Endpoint:

The primary endpoint of this trial is the Treatment Failure-Free rate at 40 week (TFF40). Treatment failure is defined as any of the following: radiographic disease progression, off-protocol treatment due to adverse event, initiation of alternative therapy (except metastatectomy post clinical benefit (CR, PR, or SD per RECIST 1.1) to treatment), and death due to any cause. Treatment failure-free rate at 40 weeks is defined as the proportion of evaluable patients who are not treatment failure at 40 weeks post randomization. All patients meeting the eligibility criteria who have signed a consent form and have received any protocol treatment will be considered evaluable. All eligible patients will be followed for disease evaluation until PD or a maximum of 2 years post-randomization then go to event monitoring for a maximum of 3 years post-randomization.

16.2 Statistical Design

16.21 Sample Size and Power:

Based on a study conducted by Motzer et. al, the median duration of pazopanib treatment was 8 month which is approximately equal to a TFF40 rate of 45%. A total of 82 eligible patients (41 in the IV ascorbic acid plus Pazopanib arm and 41 in the Pazopanib only arm) will provide 81% power to detect a 19% increase of TFF40 from 45% (in Pazopanib only arm) to 64% (in the IV ascorbic acid plus Pazopanib arm) assuming a one-sided type I error rate of 0.19 (EAST 6.4). We anticipate accruing an additional 9 patients to account for ineligibility, cancellations, and major violation for a maximum sample size of 91 patients.

16.22 Accrual Time and Study Duration:

The anticipated accrual rate is approximately 5 patients per month. Therefore, the accrual period for this randomized phase II study is expected to be 18.2. The final analysis can begin approximately 27.7 months after the trial is activated, i.e. as soon as the last patient has been observed for 40 weeks.

16.23 Operating Characteristics:

This randomized phase II design has a significance level of 0.19 when the true success proportion is 45%, and a power of 81% for detecting a true success proportion of 64%, assuming that the number of successes is binomially distributed. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as follows:

True TFF40 rate †		%‡ of times that Pazopanib+IV ascorbic acid is superior at the final analysis
Pazopanib only	Pazopanib+IV ascorbic acid	
45%	45%	18.34
45%	55%	47.93
45%	64%	79.45

‡ Proportions are based on 10,000 replicates in the simulation study

16.3 Analysis Plan

Efficacy analysis will be based on evaluable patients where evaluable patients are defined as those who are eligible, consented, and received any protocol treatment.

The primary efficacy analysis will be performed at the time at which all patients have been followed at least 40 weeks. The point estimate and confidence intervals of TTF40 will be calculated according to the approach of Duffy and Santner (1987) for each arm. TTF40 rate will be compared across arm using normal approximation with un-pooled variance. At the final analysis, if the p-value for comparison across arm is ≤ 0.19, we will reject the null hypothesis and conclude that the pazopanib+IV ascorbic acid is promising. Otherwise, the alternative hypothesis is rejected in favor of concluding that IV ascorbic acid plus Pazopanib offers no benefit relative to Pazopanib only arm.

A planned sub analysis will compare primary and secondary endpoints for patients with prior immunotherapy to those with no prior systemic therapy at the time of study entry.

16.31 Over Accrual: If more than the target number of patients are accrued, the additional patients will be used to evaluate the stopping rule or used in any decision making processes and they will be included in final point estimates and confidence intervals.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 Overall Survival

Survival time is defined as the time from randomization to death due to any cause. Patients who are alive will be censored for death at the time of last known alive. All patients meeting the eligibility criteria that have signed a consent form and begun treatment will be considered evaluable for estimation of the survival distribution. The distribution of survival time will be estimated using the method of Kaplan-Meier and be compared using log rank tests.

16.322 Progression Free Survival

Progression Free Survival is defined as the time from start of study therapy to documentation of disease progression or death, whichever comes first. Patients who are still alive and have not progressed will be censored for progression at the time of the last tumor assessment. All patients meeting the eligibility criteria that have signed a consent form and begun treatment will be considered evaluable for estimation of the survival distribution. The progression free survival distribution will be estimated using the Kaplan-Meier method.

16.323 Overall Response Rate

A tumor response is defined to be a CR or PR noted as the objective response (according to RECIST v. 1.1) All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. The best objective response rates between the two arms will be compared using a Chi-Square test.

16.324 Duration of time on pazopanib

Duration of time on pazopanib is defined as the time from initial dose of

pazopanib until the date the patient is considered off-treatment for pazopanib or death, whichever comes first. Only patients received at least 1 dose of pazopanib will be considered evaluable for this analysis. The time on pazopanib will be described using descriptive statistics.

16.325 Adverse events:

As per NCI CTCAE version 4.0,the term toxicity is defined as adverse events that are classified as either "possibly," "probably," or "definitely related" to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns within patient groups. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing.

Adverse events and toxicities will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses. The overall adverse event rates for grade 3 or higher adverse events will be compared using Chi-Square tests between the 2 treatment arms.

16.33 Analyses of Correlative Research

For each correlative research aim, the biomarker of interest (e.g. 5mC, 5hmC, etc) will be evaluated per section 17.42. The biomarker values will be summarized graphically and descriptively. The prognostic and predictive effect of each biomarker will be evaluated separately.

5hmC specific analysis plan

Hypothesis: The improvement of the primary endpoint due to the addition of ascorbic acid to pazopanib in patients with low 5hmC intensity is more than that of patients with high 5hmC intensity.

Analysis plan: For each patient, the intensity of 5hmC will be determined by IHC and categorized to one of the following category: absent, mild, moderate, and marked. For the purpose of this analysis, patients will be separated into 2 5hmC groups, high intensity (defined as moderate or marked in IHC read) vs. low intensity (defined as absent or mild in IHC read). The treatment failure-free rate at 40 week (TFF40) and corresponding confidence interval will be estimated for Arm A and B patients with low intensity and high intensity separately. Logistic regression for TFF40 will be carried out to determine the likelihood of TFF40 for Arm A vs. B in different 5hmC intensity groups by incorporating the interaction term between treatment arms and 5hmC intensity (low vs. high). The interaction term will be tested by likelihood ratio test to determine whether the differential treatment effect is statistically significant across 5hmC intensity groups (low vs. high). The p-value < 0.1 will be considered as statically significant for the test of interaction term.

16.4 Data & Safety Monitoring:

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

16.42 Adverse Event Stopping Rules:

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

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

- If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e. when accrual is greater than 10 patients) have experienced a grade 4 adverse event
- If at any time, 2 patients have experienced a grade 5 adverse event (not due to progressive disease).

16.5 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the “ClincialTrials.gov” website. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov.

- For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 27 months after the study opens to accrual.

- The definition of “Primary Endpoint Completion Date” (PECD) for this study is the time the last patient registered has been followed for at least 40 weeks.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory or optional***	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for biospecimen submission**
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (OR 10 unstained slides with 1 corresponding H&E) from primary tumor	Mandatory	≤ 30 days after registration	Correlative studies (Section 17.4.2)	Section 17.2

*Receipt of archival tumor tissue is not required for study registration and initiation of therapy. However, it is strongly recommended to receive the required tissue, if available, within 30 days from registration.

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 In patients with prior surgical resection of the primary tumor or surgical resection of a metastasis, submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of tumor. In the case of a biopsy specimen from a metastatic tumor or unresectable primary tumor, the tissue block with the largest amount of tumor should be submitted. In patients with surgical resection of the primary tumor, and material from a metastasis, a block from each specimen should be submitted.

17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 10 five-micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** H&E stain the first cut slide (i.e. slide labeled 1). These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.4.2. For needle biopsy specimens, multiple sections should be mounted onto each slide to ensure that an adequate amount of tumor tissue is available. **Do not bake or place covers slips on the slides. Do not place sticky labels on slides.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide OR *10* unstained slides with one corresponding H&E s.
- Specimen Submission: Tissue (Baseline) Form
- Surgical Pathology Report

Pathology/Operative Report *(optional).*

Note: Please include the ACCRU patient ID number on all materials listed above.

17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. During warm weather months, paraffin blocks should be shipped using refrigerant pack to avoid heat that may melt paraffin and damage blocks.

17.25 Tissue specimens must be shipped ≤**30** days after registration.

17.26 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.28 If a corresponding H&E wasn't submitted with the block/slides, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block at the IHC core facility and Mayo Clinic Rochester for quality assurance purposes.

17.29b When an appropriate request is submitted, the ACCRU Operations Office will forward the block/slides to the ACCRU Research Base Pathology Research Core, Mayo Clinic Rochester for processing as outlined in Section 17.42

17.3 Frozen Tumor tissue: None

17.4 Study Methodology and Storage Information

17.41 Submitted tissue samples will be analyzed as follows:

17.42 Correlatives:

Correlative studies will be done at the IHC core facility at Mayo Clinic Rochester and interpreted by a pathologist.

17.421 Epigenetic mechanism correlatives: 5mC, 5hmC and H3K27me3 IHC on pre-treatment biopsy on all patients who have tissue available. Oxidative bisulphite sequencing (OxBS) and RNA sequencing will be performed on 16 patients per arm. OxBS and RNA sequencing will be performed, using 3 unstained 5 micron slides (and 1 H&E slide) per patient, or a 5mm3 tissue block per patient.

17.422 H2O2 mechanism correlatives: iron in the tumor microenvironment on pre-treatment biopsy (Prussian blue stain).

17.423 HIF pathway mechanism correlatives: HIF-1 alpha, HIF-2 alpha IHC on pre-treatment biopsy.

17.424 Dehydroascorbic acid mechanism correlatives: GLUT-1 IHC on pre-treatment biopsy.

17.425 Immune mechanism: PDL1 IHC on pre- and treatment biopsy on 10 patients in both arms.

17.43 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations [redacted] for future research according to the patient consent permission (see Section 6.15). Potential future research may include IHC analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.44 Banking of tumor tissue, according to the patient consent permission (see Section 6.15), is for future research.(This collection is part of a general strategy of investigation for ACCRU studies).

17.45 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.46 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.47 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions[redacted].

18.1 Submission Timetables

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤ 2 weeks after registration
On-Study Form	
Adverse Events: Baseline	
On-Study: Prior Radiation[1]	
RECIST Measurements: Baseline	
ACCRU Deviation Form	
Supporting Documentation: Baseline	
Laboratory Tests and Results: Baseline	
Specimen Submission: Tissue (Baseline)[2]	
Patient Status: Baseline	
OP and Path Reports (see Section 17.0)[3]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit only if applicable.
2. ≤ 30 days
3. Attach an electronic copy in RAVE on the Supporting Documentation Form. This is in addition to the pathology material requirements for tissue submission (Section 17.0). **NOTE: All reports must be de-identified, and labeled with study number, ACCRU patient ID number, and initials.**

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Treatment (Intervention) Form	X[1]	X	
Treatment (Intervention):Dose modifications, Omissions, and Delays[2]	X[2]	X[2]	
Adverse Events: Solicited	X	X	
Adverse Events: Other[2]	X[2]	X[2]	
RECIST Measurements	X	X	X
Supporting Documentation[2]	X[2]	X[1]	
Laboratory Tests and Results	X	X	X
Patient Status: Treatment (Intervention)	X	X	
Off Treatment		X	
Patient Status: Clinical Follow-up/Observation			X
Ascorbic Acid and Pazopanib in Off Study Setting			X[2]
Adverse Event: Late[2]			X[2]
Consent Withdrawal[2]	X[2]	X[2]	X[2]
Consent Withdrawal: Specimen Only[2]	X[2]	X[2]	X[2]
Consent Withdrawal: Clinical Follow-Up Only[2]	X[2]	X[2]	X[2]
Consent Withdrawal: All Follow-Up[2]	X[2]	X[2]	X[2]
ACCRU Deviation Form[2]	X[2]	X[2]	X[2]

1. Attach a copy of documentation of response or progression in RAVE on the Supporting Documentation form if disease is evaluated. **NOTE: All reports must be de-identified, and labeled with study number, ACCRU patient ID number, and initials.**
2. Submit only if applicable.

Follow-up Material(s)

CRF	Event Monitoring Phase/Survival Follow-Up[1]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-up/Event Monitoring	X	X	X	X	
Supporting Documentation[2]		X			
Non-Protocol Treatment[3]	X		X		
Adverse Events: Late[3]	X		X		
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-up	X		X		
Ascorbic Acid and Pazopanib in Off Study Setting					X
Lost to Follow-up[3]	X		X		
ACCRU Deviation Form[3]					X
Notice of New Primary[3]					X

1. Patients are followed in Event Monitoring for a maximum of 3 years from registration.
2. Attach a copy in RAVE for documentation of progression on the Supporting Documentation Form. **NOTE: All reports must be de-identified, and labeled with study number, ACCRU patient ID number, and initials.**
3. Submit only if applicable.

19.0 Budget

19.1 Costs charged to patient: Each site should review the test schedule (Section 4.0) taking into account local and regional coverage policies to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Mandatory tissue collection and analysis, and G6PD (Glucose-6-phosphate dehydrogenase) test.

19.3 Other budget concerns: ASCOR® is provided free of charge to patients while they are participating on this study.

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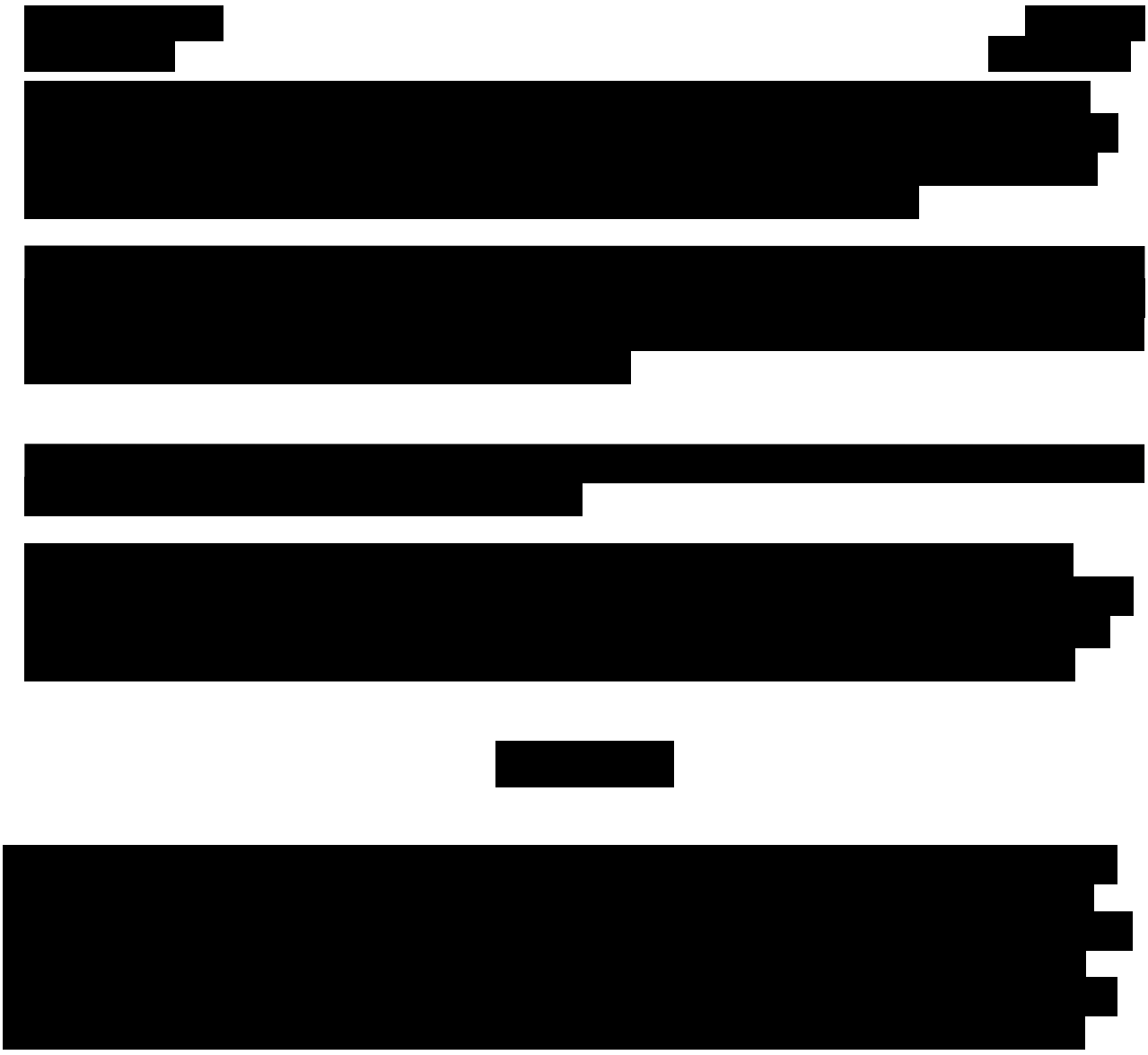

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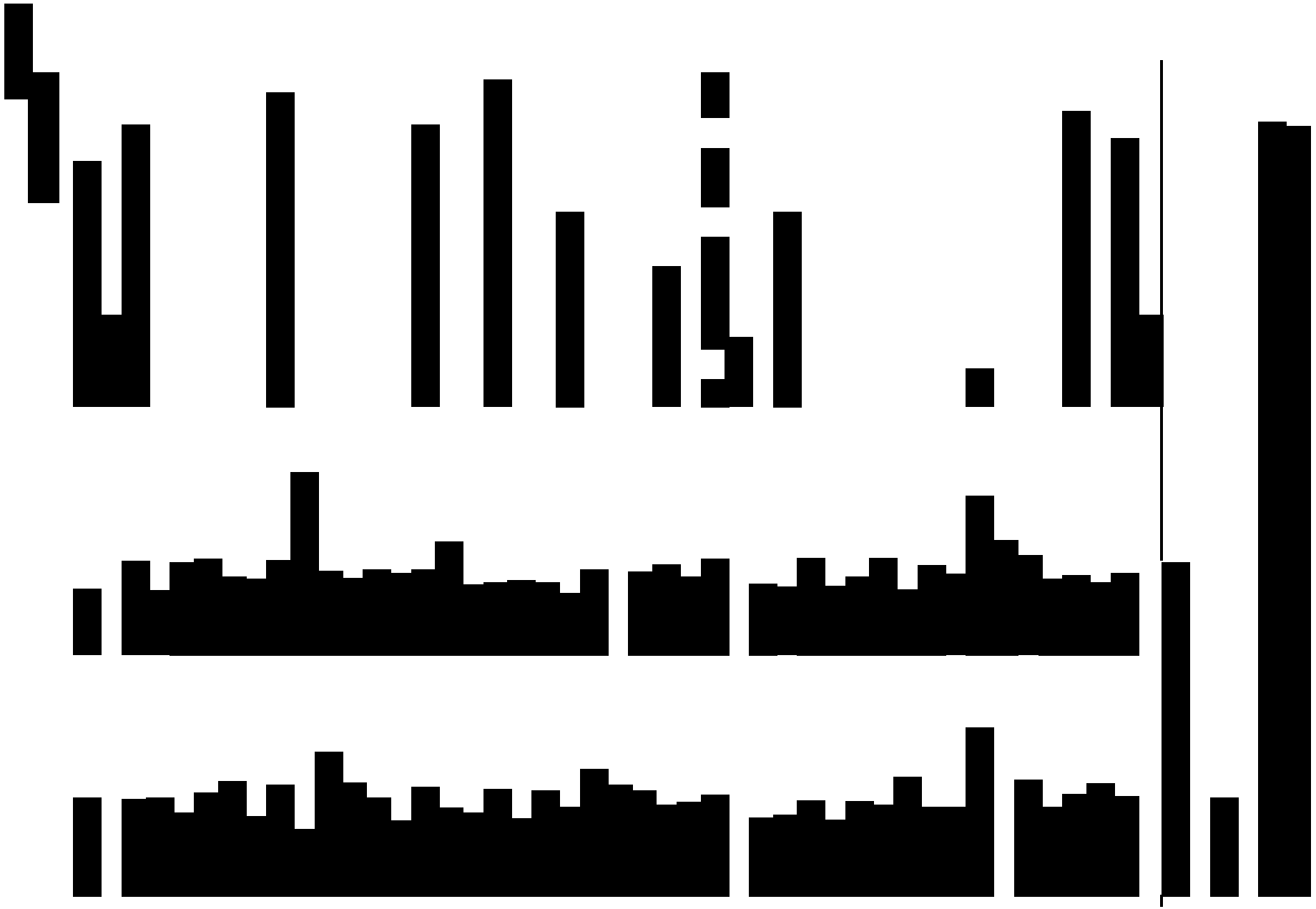

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