

PROTOCOL UMCC 2016.013
Pilot Study of Pazopanib with Low Fat Meal (PALM) in advanced renal cell carcinoma

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Study Drug: Pazopanib, sold under the brand name Votrient

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ABBREVIATIONS:

| | |
|------------|--|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CMP | Comprehensive Metabolic Panel |
| CR | Complete Response |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTO | Clinical Trials Office |
| DLT | Dose Limiting Toxicity |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| EF | Ejection fraction |
| H&P | History & Physical Exam |
| HRPP | Human Research Protections Program |
| HTN | Hypertension |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IV (or iv) | Intravenously |
| LFTs | Aspartate aminotransferase, alanine aminotransferase and total bilirubin |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| RCC | Renal Cell Carcinoma |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PI | Principal Investigator |
| PO | per os/by mouth/orally |
| PR | Partial Response |
| PRC | Protocol Review Committee |
| PPI | Proton Pump Inhibitor |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| TTE | Transthoracic echocardiogram |
| UaP | Unanticipated Problem |
| ULN | Upper Limit Normal |
| UMCCC | University of Michigan Comprehensive Cancer Center |

UPC Urine protein to creatinine
 VEGF/VEGFR Vascular endothelial growth factor/vascular endothelial growth factor receptor
 WBC White Blood Cells

STUDY SYNOPSIS

| | |
|--------------------|--|
| Title | Pilot Study of PA zopanib with Low Fat Meal (PALM) in advanced renal cell carcinoma. |
| Phase | Feasibility pilot study |
| Methodology | Open-label |
| Study Duration | 1 year of accrual. |
| Study Center(s) | Single-center |
| Objectives | <p>Primary Objectives</p> <ul style="list-style-type: none"> To determine the safety and feasibility of pazopanib given with a low fat meal for therapy of metastatic renal cell carcinoma. <p>Secondary Objectives</p> <ul style="list-style-type: none"> To determine the overall response rate to pazopanib given with a low fat diet in first-line therapy of metastatic renal cell carcinoma. To explore PK characteristics (Cmax) of pazopanib taken with a low fat meal. |
| Number of Subjects | 16 with interim analysis for safety after 8 subjects have been treated with pazopanib for at least 4 weeks. |
| Inclusion Criteria | <ol style="list-style-type: none"> Adult (>18 years old) patient with unresectable locally advanced or metastatic RCC with a clear cell component Measurable disease per RECIST 1.1 criteria No prior pazopanib therapy Subject must have ECOG PS of ≤2 Subject must be willing to take pazopanib with a low-fat meal per protocol Subjects are permitted to have had up to 3 prior VEGF or VEGFR targeted therapies, plus any number of prior cytokine therapies (e.g.IL-2) or checkpoint inhibitor therapy (e.g. anti-PD1/PDL1, anti-CTLA4) or mTOR inhibitor therapy(e.g. everolimus, temsirolimus) Platelets > 100,000 mm³, ANC > 1000 mm³ and AST/ALN < 1.5 X ULN; Total Bilirubin < 1.5 times ULN Subject must be willing to discontinue any proton pump inhibitors/strong CYP3A4 inducers or inhibitors (section 9.1) Agree to use effective contraception and stop simvastatin if on it. |

| | |
|---|--|
| <p>Exclusion Criteria</p> | <ol style="list-style-type: none"> 1. Any concurrent health condition that in the view of the treating physician would pose excessive risk to the subject if he/she is enrolled in the study. 2. Subjects with a history of hemoptysis, cerebral hemorrhage or clinically significant GI hemorrhage or myocardial infarction (MI) within the past 6 months. 3. Patients at significant risk for GI perforation or fistula. 4. Pregnant or nursing mothers. 5. Untreated CNS metastasis. If treated CNS metastasis/es, such treatment must have been completed at least 30 days prior to registration. 6. Subjects with Cirrhosis, HIV, Hepatitis B or C 7. Averaged QTc baseline in 3 ECGs at least 5 minutes apart of ≥ 450 ms. 8. Congestive Heart Failure (NYHA Class III/IV), LVEF $< 50\%$ at baseline. |
| <p>Study Product(s), Dose, Route, Regimen</p> | <p>Pazopanib 400mg (starting dose) PO daily with low-fat meal (LFM) in 14 day cycles. Pazopanib may be increased to 600 mg and subsequently to 800 mg PO with low-fat meal daily starting with second cycle if the prior dose is tolerated. Pazopanib may be decreased to 200 mg PO with low-fat meal daily starting with second cycle if the starting dose is NOT tolerated. Pazopanib dose may be adjusted every 2 weeks based on toxicities. No re-escalation of dose is allowed.</p> |
| <p>Duration of Administration</p> | <p>Until progression of disease or unacceptable toxicity or withdrawal from protocol therapy or after 6 cycles (12 weeks) of Pazopanib treatment.</p> |
| <p>Statistical Methodology</p> | <p>The feasibility and safety of Pazopanib with low-fat meal will be assessed based on the following statistics with a 95% confidence interval around the reported statistic: frequency of toxicity, severity of toxicities (according to CTCAE version 4.03 criteria), frequency of dose-reductions, duration of therapy, and mean or median total dose taken.</p> |

1.0 BACKGROUND AND RATIONALE

1.1 Background

Pazopanib is an orally administered multi-kinase inhibitor targeting VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet derived growth factor) and c-kit, which are critical to growth and proliferation of neoplastic cells. Pazopanib has been FDA approved for advanced renal cell carcinoma (RCC) with a clear cell component. This approval was based on phase 3 clinical trial results in adult patients with measurable, locally advanced, and/or metastatic RCC with either no prior therapy or one prior cytokine therapy randomly assigned 2:1 to receive oral pazopanib (800 mg once daily on an empty stomach) or placebo¹. The primary end point was progression-free survival (PFS). Secondary end points included overall survival, objective tumor response rate (RECIST criteria) and safety. Of the 435 patients enrolled, 233 were treatment naive (54%) and 202 were cytokine pretreated (46%). Progression free survival was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; $P < .0001$). In pre-planned subset analyses, pazopanib prolonged PFS in both treatment-naive subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; $P < .0001$), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; $P < .001$). The objective response rate was 30% with pazopanib compared with 3% with placebo ($P < .001$), with a median duration of response longer than 12 months on pazopanib¹.

In a subsequent non-inferiority trial, pazopanib was compared to sunitinib in therapy of clear cell metastatic renal-cell carcinoma, in 1110 patients who were randomized in a 1:1 manner to receive continuous pazopanib (800 mg once daily on an empty stomach; 557 patients) or sunitinib in 6-week cycles (50 mg once daily for 4 weeks, followed by 2 weeks without treatment; 553 patients)². The primary end point was progression-free survival as assessed by independent review, and the study was powered to show non-inferiority of pazopanib versus sunitinib. Secondary end points included overall survival, safety, and quality of life. Pazopanib was shown to be non-inferior to sunitinib with respect to progression-free survival (hazard ratio for progression of disease or death from any cause, 1.05; 95% confidence interval [CI], 0.90 to 1.22), meeting the predefined non-inferiority margin (upper bound of the 95% confidence interval, <1.25). Overall survival was also similar (hazard ratio for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08). Patients treated with sunitinib, as compared with those treated with pazopanib, had a higher incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%). Patients treated with pazopanib had a higher incidence of increased levels of alanine aminotransferase (60%, vs. 43% with sunitinib). The mean change from baseline in 11 of 14 health-related quality-of-life domains, particularly those related to fatigue or soreness in the mouth, throat, hands, or feet, during the first 6 months of treatment favored pazopanib ($P < 0.05$ for all 11 comparisons)².

Pazopanib has since become one of the standard first line therapies in metastatic RCC³. If other agents are chosen in the first line setting, pazopanib is often used in subsequent lines of therapy.

Pazopanib Dosing

Conventional Pazopanib dosing WITHOUT FOOD is with an initial dose of 800 mg PO qday, with subsequent dose-reduction to 400mg or 600 mg daily as needed for toxicities. Pazopanib is routinely administered by mouth at least 1 hour before or at least 2 hours after food per the FDA approved package insert. These instructions are primarily to keep absorption of the medication fairly constant from one day to the next. When given as specified in the package insert, absolute bioavailability of the drug is only 21%. It is well known that fat in a meal co-administered with pazopanib results in higher absorption of the drug. Administration of pazopanib with a low or high fat meal has been studied in an

open-label, randomized, crossover, phase I study that evaluated the effect of low- and high-fat meals on the pharmacokinetics (PK) of pazopanib in patients with advanced solid tumors⁴. Pazopanib is highly lipophilic, and therefore high fat meals can either potentiate the absorption of pazopanib, or reduce its solubility by stimulating gastric acid synthesis⁴. Six subjects were enrolled in a lead-in cohort. They received a single dose of pazopanib 400 mg with a high-fat meal and were then monitored for safety for 8 days. Twenty-nine patients were then enrolled in the food-effect cohort and then randomized to receive two single doses of pazopanib 800 mg in either the fed condition (high- or low-fat meal) or fasting condition, in random sequence 14 days apart. After completion of the study, patients were given the opportunity to continue treatment with daily pazopanib 800 mg in the fasting state. Administration of pazopanib with either low- or high-fat meals had resulted in a similar magnitude of increase in the maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of approximately twofold as compared with the corresponding values when administered to patients in the fasted condition⁴.

Pharmacokinetic studies have shown that pazopanib doses greater than 800mg daily in the fasting state did not increase systemic exposure of pazopanib at steady state, likely due to saturation of absorption in the gut⁴. Therefore, it is unclear at this time whether the increased C_{max} and AUC of pazopanib when given with food will correlate with higher systemic exposure when these doses are given repeatedly daily with food. Furthermore, although C_{max} and AUC were increased, the half-life of the drug was the same in patients who received pazopanib fasting or with food, indicating that administering pazopanib with food primarily affects its bioavailability⁴. This study did not control for the content and volume of meals the participants ate, and did not perform pharmacokinetic studies on continued dosing of pazopanib with food.

Administration of pazopanib with food in the context of varying day to day diets could indeed result in excessive variability of absorption and systemic levels of the drug. But if pazopanib could be taken with meals of similar fat content daily, higher and fairly consistent absorption of the drug may possibly be achieved safely, potentially translating into equivalent or improved efficacy of pazopanib with smaller quantities of the drug compared to standard administration without food and with an acceptable safety profile.

1.2 Study Rationale

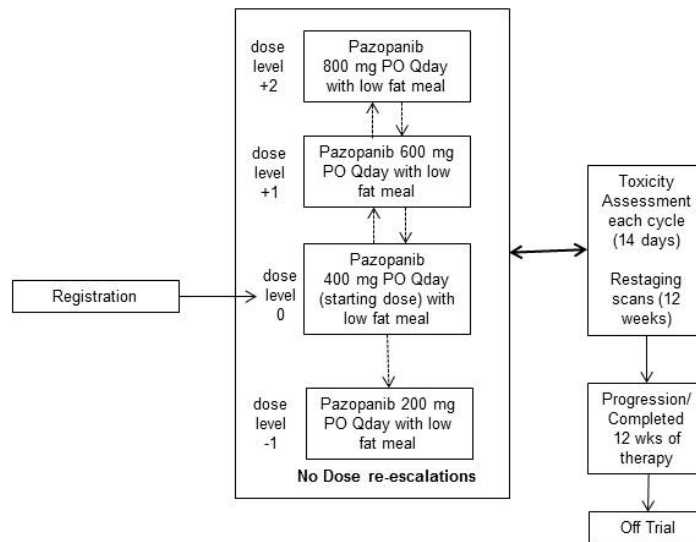
- 1) Increased efficacy: Administration of pazopanib with a consistent meal containing a standard low quantity of fat every day could result in higher systemic levels of the drug with low intra-patient variability, translating into higher efficacy against advanced renal cell cancer.
- 2) Lower cost: A similar strategy with abiraterone acetate in castration resistant prostate cancer was recently reported and sets a precedent for our approach⁵. If our approach is shown to be feasible and safe, future strategies could allow intake of similar amounts of the drug to achieve similar or greater efficacy as in the fasting state, resulting in substantial cost savings given its high cost of the medication. For example, abiraterone when taken with food could result in savings of \$3,750 per month per patient at current prices. Assuming patients would only need approximately half the quantity of drug as currently used (given the 2-fold increase in C_{max} and AUC), the potential for cost savings with pazopanib given with low fat diet could be approximately \$3,890 per month per patient at current prices.
- 3) Convenience: Intake of the drug with food also minimizes the practical inconvenience of taking pazopanib in the fasting state.

We hypothesize that administration of pazopanib with low fat meal would be safe and feasible with secondary implications of higher pazopanib levels; potentially translating into greater anti-tumor efficacy in advanced renal cell cancer, with significant cost savings. In the proposed pilot study, we seek to test the feasibility and practicality of this approach and gather preliminary data on adverse effects and the safety profile. We hope to ameliorate any potential for greater toxicities with a dynamic dosing design that incorporates adverse events from each cycle into dosing for the next cycle and a structured symptom specific plan.

1.3 Study Design/Schema

Registered subjects will take pazopanib by mouth with a low-fat meal (**containing less than 400 calories and less than 20% fat or 10 grams per meal**) approximately, some sample meals are described in appendix 1) every day in 14 day cycles, for a total of 6 cycles, with a starting dose of 400 mg and adjusted for the next cycle (dose level +1: 600 mg; dose level +2: 800 mg; dose level -1: 200 mg) based on toxicity assessment during or at the end of each cycle. No dose re-escalations are permitted. Imaging will be performed post 12 weeks of treatment.

An interim analysis for safety will be performed after 8 subjects have completed at least 2 cycles (4 weeks) of therapy.



2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- 2.1.1 To assess the safety and feasibility of pazopanib administered with a low fat meal in therapy of advanced renal cell carcinoma

2.2 Secondary Objectives

- 2.2.1 To estimate the efficacy of pazopanib administered with a low fat meal in therapy of advanced renal cell carcinoma.
- 2.2.2 To explore PK characteristics (Cmax) of pazopanib taken with a low fat meal.

2.3 Endpoints

2.4 Primary Endpoint:

- 2.4.1 To assess the frequency of grade 3 or 4 adverse events associated with pazopanib administered with a low fat meal by CTCAE ver 4.0.

2.5 Secondary endpoints:

- 2.5.1 To estimate the overall response proportion to pazopanib administered with a low fat meal by RECIST 1.1 criteria.
- 2.5.2 To explore Cmax in subjects treated with pazopanib administered with a low fat meal and its potential correlation with toxicity as assessed by CTCAE ver 4.0

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled on the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

- 3.1.1 Adult (>18 years of age) with unresectable locally advanced or metastatic renal cell carcinoma with a clear cell component.
- 3.1.2 Subjects must have measurable disease per RECIST 1.1 criteria.
- 3.1.3 Subjects must not have had prior pazopanib therapy.
- 3.1.4 Subjects must have an ECOG PS of < 2.
- 3.1.5 Up to 3 lines of prior VEGF or VEGFR targeted therapy are permitted. Any prior therapy should have been completed ≥ 2 weeks prior to start of study therapy.
- 3.1.6 Subjects may have received any number of the following therapies: cytokine therapy (e.g. high dose interleukin-2) or checkpoint inhibitor therapy (e.g. anti-PD1/PDL1, anti-CTLA4) or mTOR inhibitor therapy (e.g. everolimus, temsirolimus).

3.1.7 Adequate organ and marrow function as defined below:

| | |
|---------------------------|---|
| ANC | > 1000/mm ³ |
| Platelets | > 100,000/mm ³ |
| AST, ALT, Total bilirubin | < 1.5 X ULN. Patients with Gilbert's disease are exempt from this criteria (please see dose-adjustment for Gilbert's as per table 3). |

3.1.8 Subject must be willing and able to take pazopanib with a low-fat meal every day as specified in the protocol.

3.1.9 Subjects must be willing and able to come off any PPI/other strong CYP3A4 inhibitors or inducers/simvastatin.

3.1.10 Ability to understand and the willingness to sign a written informed consent.

3.1.11 All subjects, including those who are surgically sterilized, must be willing to use an effective method of contraception (barrier method of birth control or abstinence) from the time informed consent is signed until 6 months after completion of protocol therapy.

3.2 Exclusion Criteria

3.2.1 Any concurrent health condition that in the view of the treating physician would pose excessive risk to the patient if enrolled in the study.

3.2.2 Subjects with a history of significant hemoptysis per the treating physician's judgment, cerebral hemorrhage or clinically significant GI hemorrhage or myocardial infarction (MI) within the past 6 months.

3.2.3 Patients at significant risk for GI perforation or fistula.

3.2.4 Pregnant or nursing mothers.

3.2.5 Untreated CNS metastasis. If treated CNS metastasis/es, treatment of CNS disease (surgery or radiation) must have been completed at least 30 days prior to registration. Patients could still be on steroids.

3.2.6 Subjects with known history of Cirrhosis, HIV, Hepatitis B or C.

3.2.7 Averaged QTc baseline in 3 ECGs at least 5 minutes apart of ≥ 450 ms.

3.2.8 Congestive Heart Failure (NYHA Class III/IV) or LVEF <50% at baseline.

3.2.9 Uncontrolled hypertension (HTN) despite medical management (Blood pressure (BP) $\geq 160/100$).

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Subjects will be recruited from the routine clinical practice of the treating oncologists. After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Clinical Trials Office. The patient will not be considered registered and enrolled in the study until all information is confirmed by the Clinical Trials Office Data Manager.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within seven business days of registration to the study.

Subjects will take starting dose of pazopanib 400 mg PO once a day with a low-fat meal as specified in the protocol once daily in every 14 days cycles, for a maximum of 12 weeks.

Consecutive doses should be taken approximately 24 hours (\pm 4 hours) apart.

If the subject does not develop significant toxicities as described in Section 5.2 after the first cycle, then the pazopanib dose will be escalated to 600 mg PO once daily with low-fat meal for the next cycle. If the subject does not develop significant toxicities as described in Section 5.2 at 600 mg, then the pazopanib dose will be escalated to 800 mg PO once daily with low-fat meal for the next cycle.

Subject will be assessed for significant toxicities as described in section 5.2 at the end of each cycle by clinical exam and laboratory values including liver function tests. Any grade 3 or 4 pazopanib-related (as assessed by treating investigator) non-hematological toxicities (except specific toxicities listed in table 2, 3 and 4) will necessitate dose reduction by 1 dose level for the next cycle.

No dose re-escalations are permitted.

Table 1 Pazopanib Dose Levels in Study

| Dose Level | Pazopanib with low fat meal |
|------------|-------------------------------------|
| +2 | 800 mg daily |
| +1 | 600 mg daily |
| 0 | 400 mg daily (starting dose) |
| -1 | 200 mg daily |

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives at least 1 dose of pazopanib on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.5). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Dose adjustments should be made according to the system showing the greatest degree of toxicity. Please see tables 2, 3, 4, 5 for dose adjustment criteria.

Note:

- Subjects will be removed from the trial if treatment is held for 4 weeks or longer continuously.
- To avoid potential wound healing complications, Pazopanib should be discontinued 5 days prior to any surgery and restarted based on the clinical judgment of the primary physician caring for the wound post-operatively.

Any pregnancies occurring up to 6 months after completion of protocol therapy will be reported to IRBMED.

Table 2: Dose-adjustment of pazopanib for hematological toxicities.

| Hematological Toxicity Dose Reductions for Pazopanib | | |
|---|------------------|---|
| ANC¹ | Platelets | Action |
| ≥ 1,000/ μ L or | ≥50,000/ μ L | None. |
| <1,000/ μ L or | <50,000/ μ L | Hold drug until ANC ≥ 1,000/ μ L and platelets ≥ 50,000/ μ L. Restart at one dose level lower. If already at lowest dose level (-1), discontinue pazopanib. |

Table 3: Dose–reductions of pazopanib for specific non-hematological toxicities.

| Example of Non-Hematological Toxicity Dose Reductions | |
|--|--|
| Event | Action |
| Liver toxicity | |
| Normal total bilirubin with any degree of ALT elevation or total bilirubin <1.5x ULN | None |
| Isolated AST/ALT elevations between 3-8 x ULN with total bilirubin ≤ 2x ULN | Continue pazopanib without dose reduction, but monitor AST/ALT weekly until ALT returns to grade 1 (NCI CTCAE version 4) or baseline. |
| Isolated ALT >8x ULN with total bilirubin less than or equal to 2x ULN | Hold pazopanib and monitor ALT/AST weekly until ALT returns to grade 1 (NCI CTCAE version 4) or baseline. At this time, can restart pazopanib at 400mg daily. Continue measuring AST/ALT levels weekly for at least 8 more weeks. If hepatotoxicity is to recur during this period, discontinue pazopanib permanently and remove the subject from trial. |
| ALT ≥ 3x ULN AND total bilirubin >2x ULN | Discontinue pazopanib permanently and monitor LFTs weekly until they return to grade 1 (NCI CTCAE version 4) or baseline. |
| ALT/AST >3x ULN with known or suspected Gilbert with mild indirect hyperbilirubinemia (total bilirubin ≤ 6mg/dL and direct bilirubin <35% of total). | Continue pazopanib without dose reduction, but monitor AST/ALT weekly until ALT returns to grade 1 (NCI CTCAE version 4) or baseline. |
| Hypertension | |
| Grade 1: (pre-hypertension with systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg) | None. Blood pressure should be monitored as recommended by the treating physician. |

| | |
|---|---|
| <p>Grade 2: Persistent (>24 hours) or recurrent HTN (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg) or symptomatic BP increase by >20 mmHg diastolic or >140/90 mmHg if previously within normal limits.</p> | <p>Initiate monotherapy with anti-hypertensive agent of treating physician's choice belonging to the Calcium channel blocker (CCB) or ACE I/ARB class to lower BP back down to goal of systolic less than 140 mmHg and diastolic less than 90 mmHg. Blood pressure should be monitored as recommended by the treating physician and dose adjustment of pazopanib as per judgment of treating physician but is not mandated.</p> |
| <p>Grade 3: Systolic BP > 160mmHg or diastolic >100mmHg or medical intervention indicated</p> | <p>Initiate more anti-hypertensive medications or intensive anti-hypertensive therapy with agents of treating physician's choice to bring subject's BP back to goal of systolic < 140 mmHg and diastolic < 90 mmHg. Blood pressure should be monitored as recommended by the treating physician and dose adjustment or discontinuation of pazopanib as per judgment of treating physician.</p> |
| <p>Grade 4: life-threatening HTN (i.e. malignant HTN or posterior reversible encephalopathy syndrome (PRES))</p> | <p>Discontinue Pazopanib permanently.</p> |
| <p>QTc Prolongation</p> | |
| <p>QTc interval \geq 500msec or > 60msec from baseline QTc interval on averaged 3 ECGs taken at least 5 minutes apart</p> | <p>Check concurrent medications for causes of QTc prolongation and if considered contributing, discontinue them.</p> <p>Check electrolyte levels in serum including magnesium, potassium and calcium.</p> <p>Continue study drug at 1 dose level lower and recheck ECG x 3 five minutes apart on next visit. If already at -1 dose level, then discontinue pazopanib.</p> |
| <p>Proteinuria</p> | |
| <p>Urine Protein Creatinine ratio (UPC ratio) >1 but <3</p> | <p>Obtain 24 hour urine protein and if <3g, continue at current dose and monitor as clinically indicated.</p> |
| <p>Urine protein UPC ratio \geq 3 and/or urine protein in 24 hr urine protein \geq 3g/dL/1.73 m²</p> | <p>Discontinue pazopanib and obtain weekly UPC or 24 urine protein until UPC ratio <3 or 24 hour urine protein is <3g/dL/1.73 m² BSA. Then, can restart pazopanib with a one level dose reduction.</p> <p>If no further dose reductions in pazopanib can be made, then discontinue pazopanib.</p> |

| | |
|---|--|
| Nephrotic syndrome | Discontinue pazopanib |
| LV dysfunction or CHF | |
| Grade 1 and 2 | None |
| Decline in LVEF greater $\geq 15\%$ or EF is $< 50\%$. | Stop pazopanib, repeat TTE in 8 weeks and if either of these (decline in LVEF greater $\geq 15\%$ or EF is $< 50\%$) are confirmed, refer to cardiology to institute CHF measures such as beta-blocker, ACEI/ARB etc. |
| Symptomatic heart disease or CHF | Refer to cardiology and discontinue pazopanib permanently if alternative causes are not found. |

Table 4. Management of other specific adverse events.

| Event | Action |
|----------------------------------|---|
| Hemorrhage/bleeding | |
| Grade 1 | None, except if hemoptysis, in which case the PI should be contacted to determine whether continuation of therapy is appropriate. |
| Grade 2 | If non-pulmonary, hold pazopanib until resolves to grade 1 or less. Then can restart pazopanib with a one dose level dose-reduction. If already at (-1 dose level), discontinue pazopanib permanently. If pulmonary, the PI should be contacted to determine whether continuation of therapy is appropriate. |
| Grade 3 or 4 | Discontinue pazopanib permanently |
| Arterial thrombosis | |
| All grades | Discontinue pazopanib permanently |
| GI fistula or perforation | |
| All events | Discontinue pazopanib permanently |

Table 5: Pazopanib dose-adjustments based on other unspecified non-hematological toxicity grade per NCI CTCAE version 4.0.

| NCI CTCAE Grade | Pazopanib |
|-----------------|--|
| 0-2 | No change from original starting dose (except liver toxicity as described in Table 3) |
| 3 -4 | Hold until resolved to \leq Grade 2, then resume with 1 dose level reduction. |

5.3 Concomitant Medications/Treatments

Patients should avoid PPI or other drugs that inhibit (i.e. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, voriconazole) or induce (i.e. rifampin) CYP3A4. Specifically, taking pazopanib with simvastatin has showed to increase the risk of hepatotoxicity. So, **simvastatin has to be stopped prior to/at subject registration.**

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment as deemed appropriate by treating physician.
- Unacceptable adverse event(s) as defined in Section 8.0

- Patient voluntarily withdraws from treatment OR changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Completion of therapy with pazopanib with low fat meal for 12 weeks. Patients could then go onto standard therapies, including pazopanib given without food/low fat meal.

5.5 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.4 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.6 Duration of Follow-Up

Patients will be followed for 28 days after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event (Grade 1 or lower).

5.7 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- 5.7.1 Patient withdraws consent (termination of treatment and follow-up);
- 5.7.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- 5.7.3 Patient is unable to comply with protocol requirements;
- 5.7.4 Treating physician judges continuation on the study would not be in the patients best interest;
- 5.7.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- 5.7.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment or which would interfere with this study (per PI);
- 5.7.7 Termination of the study by The University of Michigan;
- 5.7.8 Patient completes protocol treatment and follow-up criteria.

5.8 Patient Replacement

Subjects who are removed or withdraw consent from the study will not be replaced.

6.0 STUDY PROCEDURES

6.1 Pharmacokinetic Assessment

Analysis of the samples for plasma concentration of pazopanib by the Pharmacokinetics Core at the College of Pharmacy of the University of Michigan at various time points (please refer to Section 10.0 for details) will be per previously established assays⁶.

6.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

6.2.1 *Informed Consent*

6.2.2 *Medical history*

Complete medical and surgical history, history of infections

6.2.3 *Demographics*

Age, gender, race, ethnicity

6.2.4 *Review subject eligibility criteria*

6.2.5 *Review previous and concomitant medications*

6.2.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

6.2.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix 4.

6.2.8 *Adverse event assessment*

Baseline adverse events will be assessed. See Section 8.0 for Adverse Event monitoring and reporting.

6.2.9 *Hematology*

Complete blood count with differential, platelet count.

6.2.10 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate, magnesium), glucose, and total bilirubin.

6.2.11 *Pregnancy test (for all females)*

Urine or serum.

6.2.12 *Tumor assessment*

To be performed with computed tomography or MRI of chest, abdomen and pelvis; CT or MRI of the brain.

For all axial imaging studies, intravenous contrast administration is preferred if judged safe by treating investigator.

6.2.13 **Other**

- A baseline transthoracic echocardiogram will be obtained to assess baseline LVEF
- 12-lead ECG will be obtained in triplicate at least 5 minutes apart from each other to determine QTc interval at baseline.
- A Urine Protein Creatinine ratio and TSH will also be obtained to evaluate for baseline proteinuria and hypothyroidism, respectively, as part of screening for the study.
 - Whole blood sample (10 mL) into EDTA-containing blood collection tube to be stored at the "Sample Preservation Freezer Facility"

6.3 **Procedures During Treatment**

6.3.1 **Day 1 of each cycle (e.g. C1 D1, C2 D1...etc. until C6 D1)**

- Physical exam, vital signs
- Hematology: Complete blood count with differential, platelet count.
- Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, and bicarbonate, magnesium), glucose, and total bilirubin.
- Review of toxicities (refer to section 5.2).
- Review of concomitant medications.
- 12-lead ECG will be obtained in triplicate at least 5 minutes apart from each other to determine QTc interval.

6.3.2 **Procedures for Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 ONLY**

- Patient will be given pazopanib to take by mouth with low fat meal by research/MCRU staff who will record time.
- Whole blood samples (5mL each) will be collected from patient into EDTA-containing blood collection tubes at specified times per section 10.0.

6.3.3 **EOT visit (end of cycle 6 ± 7 days)**

- End of Treatment (EOT) visit will be post 12 weeks of protocol therapy
- CT chest, abdomen, pelvis with or without intravenous contrast (with intravenous contrast preferred if clinically felt safe to do so by treating investigator). MRI abdomen pelvis can be substituted for CT abdomen pelvis.
- A repeat transthoracic echocardiogram will be obtained **once** to re-assess LVEF after 12 weeks of therapy.
- A Urine Protein Creatinine ratio and TSH will also be obtained to evaluate for baseline proteinuria and hypothyroidism, respectively, as part of screening for the study. If TSH is abnormal, add-on labs of free T3 and free T4 may be added to blood sample per treating investigator discretion.
- 12-lead ECG will be obtained in triplicate at least 5 minutes apart from each other to determine QTc interval.
- Whole blood sample (10 mL) into EDTA-containing blood collection tube to be stored at the "Sample Preservation Freezer Facility"

6.3.4 **28 days after EOT visit (± 7 days)**

- Physical exam, vital signs

- Hematology: Complete blood count with differential, platelet count.
- Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate, magnesium), glucose, and total bilirubin
- Toxicity check

6.4 Time and Events Table/Study Calendar

| Study Calendar | Screening (within 28 d) | C1 D1 ± 3d | C2 D1 ± 3d | C3 D1 ± 3d... | C4/5/6 D1 ± 3d | EOT ±7d | 28 days after EOT ± 7d |
|--|-------------------------|------------|------------|---------------|----------------|-------------------|------------------------|
| Informed Consent | X | | | | | | |
| History and PE Weight | X | X | X | X | X | X | X |
| ECOG Performance Status | X | X | X | X | X | X | X |
| Toxicity Assessment | X | X | X | X | X | X | X |
| Patient Diaries (blood pressure logs and pill diary) | X | X | X | X | X | X | |
| Dietician visit | | X | | | | | |
| CBC with differential, platelet count | X | X | X | X | X | X | X |
| COMP | X | X | X | X | X | X | X |
| TSH | X | | | | | X | |
| Concomitant Medication Review | X | X | X | X | X | X | X |
| 12-lead ECG in triplicate | X | X | X | X | X | X | |
| Transthoracic Echocardiogram with LVEF estimation | X | | | | | X | |
| PK samples* | | X | X | X | | | |
| Blood sample for storage at SPFF | X | | | | | X | |
| Urine Protein Creatinine ratio | X | | | | | X | |
| CT chest, abdomen, pelvis | X | | | | | X | |
| CT or MR head | X | | | | | X (if clinically) | |

| | | | | | | | |
|-----------------------------|---|---|--|--|--|---------------|--|
| | | | | | | indicat ed | |
| Pregnancy Test** | X | | | | | | |
| Pazopanib with low fat meal | | X | | | | | |

*Please refer to section 10.0

**Serum or urine pregnancy test for all females

*** Sample Preservation Facility (U of M- MSRB3) .

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee]. The largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first dose of study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least 4 cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤ 5 mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and 28 days post therapy, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered may be defined in the protocol when appropriate.

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

7.1.3 **Guidelines for Evaluation of Measurable Disease**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

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

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

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

7.1.4.3 Evaluation of Best Overall Response

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

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Response for this Category Also Requires: |
|----------------|--------------------|-------------|------------------|--|
| CR | CR | No | CR | ≥4 wks. confirmation |
| CR | Non-CR/SD | No | PR | ≥4 wks. confirmation |
| PR | Non-PD | No | PR | |
| SD | Non-PD | No | SD | documented at least once ≥4 wks. from baseline |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD* | Yes or No | PD | |
| Any | Any | Yes | PD | |

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

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient’s response will be assessed prior to the surgery.

7.1.5 Duration of Response

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

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

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

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from registration to time of progression.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug (pazopanib). The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (<http://ctep.cancer.gov/reporting/ctc.html>) and modified criteria for hematologic adverse events.

8.0 ADVERSE EVENTS

8.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator’s Brochure or Study Agent Prescribing Information for pazopanib. (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Votrient/pdf/VOTRIENT-PI-MG.PDF).

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment through 30 days after the last dose of study treatment or study intervention. Any serious adverse event that occurs more than 30 days

after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

8.3 Definitions

8.3.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.3.2 Serious Adverse Event

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

- **Death**
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **A life-threatening adverse event**
An adverse even is considered 'life-threatening' if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours.**

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event
Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient’s medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.3.3 Expected Adverse Events

An adverse event (AE) is considered “expected” if:

- For approved and marketed drug, such as pazopanib, those adverse events are described in the approved Package Insert (Label).
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 Unexpected Adverse Event

An adverse event (AE) is considered “unexpected” if it is not described in the Package Insert, Investigator’s Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

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

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment.

Probable – The AE *is likely related* to the study treatment.

Possible – The AE *may be related* to the study treatment.

Unlikely – The AE *is doubtfully related* to the study treatment.

Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Serious Adverse Event Reporting Guidelines

- 8.5.1 The Principal Investigator must be notified within 1 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- 8.5.2 The investigator must report all events meeting the criteria and definition of a serious adverse event(s) that are unexpected and possibly related (definite, probable or possible) to study treatment administration to the local IRB within 7 calendar days if death or life threatening, and within 14 calendar days for all others.
- 8.5.3 All Serious Adverse Events that are unexpected and possibly related (definite, probable or possible) to study treatment administration will be reported to the IRB using the CTO Serious Adverse Event form.
- PI needs to be notified of all SAEs within 1 business day- contact information is below:

Ajjai Alva, MD
University of Michigan
1500 E. Medical Center Drive
Ann Arbor, MI 48109
Phone: (734) 936-0091
Fax: (734) 615-2719
Email: ajjai@med.umich.edu
 - The study will comply with the regulations found in 21 CFR 312.32 regarding IND safety reports.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, 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.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and

3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.8 Stopping Rules for the Study at Interim Analysis

- Please refer to section 11

9.0 DRUG INFORMATION

9.1 Pazopanib

- Brand name: Votrient
- Description: 200 mg capsule-shaped, gray tablets dispensed in bottles with 120 tablets.
- Classification: Inhibitor of multiple tyrosine kinases
- Mode of action: Inhibition of VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet derived growth factor) and c-kit,
- Pharmacokinetics: Pazopanib is routinely administered without food i.e. at least 1 hour before or 2 hours after a meal (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Votrient/pdf/VOTRIENT-PI-MG.PDF). When thus administered WITHOUT food, pazopanib has a median absolute bioavailability of 21% and mean half-life of 30.9 hours. The median time to peak concentration is 2-4 hours after dose, and repeated daily dosing results in 1-4 fold increase in AUC and Cmax with a daily dose up to 800mg daily. Doses above 800mg daily did not show a consistent increase in AUC and Cmax. Administration with food results in about 2 fold increase in AUC and Cmax. Crushing the tablet also resulted in increased AUC, increased Cmax and decreased Tmax when compared to administration of the tablet as a whole. Based on these observations, it was recommended that pazopanib be administered as a whole tablet 1 hour before or 2 hours after a meal. Additionally, the bioavailability of pazopanib is affected by drugs that increase gastric pH, such as esomeprazole, resulting in reduce plasma concentration of pazopanib.

Once absorbed, pazopanib is highly bound to albumin (~99%) with no concentration dependence in the 10-100 microgram/milliliter range, and a subsequent small volume of distribution (<40% total body water). It is a substrate for human P-gp and human BCRP transporters, which mediate the efflux of substrates from cells in tissues such as small intestine, blood-brain barrier, testes and liver. Therefore, any factors that influence these transporters will also influence the tissue distribution of pazopanib. Furthermore, pazopanib is not a highly metabolized drug, as evidenced by low concentration of metabolites in vivo (<10% of parent drug concentration), and therefore pazopanib is the active drug and the major circulating species. Pazopanib does have 4 metabolites, GSK1268997, GSK1268992, GSK1071306 and GW700201, of which only GSK1268997 was active with similar inhibition of VEGF-induced endothelial receptors as pazopanib. Primary route of pazopanib metabolism is hepatic, and it is thereby excreted through the feces. Less than 4% of administered dose is excreted renally. CYP3A4 is the major metabolizing enzyme, with minor contributions from CYP1A2 and CYP2C8. Routes of metabolism are mono-

oxygenation, dioxygenation and potential oxygenation of a methyl group to a carboxylic acid. Glucuronidation was also detected in human hepatocytes. Steady-state plasma concentrations were reached by 10 days of repeated dose administration. Pharmacokinetics of pazopanib was otherwise not affected by age, race, gender, body weight and creatinine clearance.

- Side effects: Please refer to pazopanib's package insert (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Votrient/pdf/VOTRIENT-PI-MG.PDF) for a comprehensive list of adverse events.
- **Drug Interactions:** Strong inhibitors of CYP3A4, P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), all three of which include pazopanib as a substrate, should be avoided due to risk of increased toxicity associated elevated levels of pazopanib. Ketoconazole is an inhibitor of both CYP3A4 and P-gp. Lapatinib is a weak inhibitor of CYP3A4, Pgp and BCRP, and has been shown to increase pazopanib concentrations. Examples of strong CYP3A4 inhibitors are itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole. Grapefruit juice may also increase plasma levels of pazopanib through the same mechanism. Strong CYP3A4 inhibitors should be avoided.

On the other hand, CYP3A4 inducers, such as rifampin, may decrease pazopanib plasma levels, and therefore an alternative medication to rifampin is also recommended. *In vitro* studies showed pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2E1 and potentially induced CYP3A4. Pazopanib 800mg daily has no clinically relevant effect on pharmacokinetics of caffeine (CYP1A2), warfarin (CYP2C9 substrate) or omeprazole (CYP2C19 substrate) in clinical pharmacology studies. Concomitant administration of pazopanib with midazolam (CYP3A4 substrate) and dextromethorphan (CYP2D6 substrate) resulted in an increase in the AUC and C_{max}, and increase in urine dextromethorphan to dextrorphan concentrations, respectively. Pazopanib also increased the AUC and C_{max} of paclitaxel when administered concurrently.

Pazopanib is also a potent inhibitor of UGT1A1 and OATP1B1, and therefore may increase the concentrations of drugs primarily metabolized by these enzymes. One such drug is irinotecan, which also has an active metabolite, SN-38, that is metabolized by OATP1B1 and several UGT enzymes. Co-administration of irinotecan and pazopanib resulted in increased concentrations of irinotecan and its active metabolite SN-38.

- Storage and stability: Pazopanib should be stored at room temperature between 20 and 25 degrees Celsius, with excursions permitted to 15 to 30 degrees Celsius.
- Preparation and Dispensing: Pazopanib is dispensed in a bottle and may be repackaged to a pill dispenser bottle.
- Administration:
 - Pazopanib will be administered with a **low-fat meal, defined as a meal containing less than 400 calories and less than 20% fat or 10 grams per meal**, once daily orally.
 - All pazopanib pills for the day must be taken together.
 - Patient compliance with drug administration will be assessed at each visit through a pill diary that will record rate, time of pazopanib intake, number of pills, and if low fat meal was eaten.

- Availability: commercially available
- Return and Retention of Study Drug: Patients may keep their supply of pazopanib as it will not be supplied by the study. They should dispose of any unused pazopanib after their therapy course is complete or if their supply has expired by returning it to their local pharmacy. It should not be thrown in household garbage or disposed of in wastewater
- Drug Accountability: None, pazopanib is a current standard of care for metastatic renal cell carcinoma and therefore will be billed and provided as such.

10.0 Correlatives:

Pharmacokinetics:

A published, validated assay has been established at the Pharmacokinetics Core, College of Pharmacy at the University of Michigan to determine plasma pazopanib concentrations from these samples⁶.

- Patient to take the whole dose of pazopanib by mouth with low fat meal and record time of intake.
- Blood samples (6 mL drawn in EDTA tube) will be placed on ice and centrifuged within 10 minutes of collection, for 10 minutes at 2,000 x g for fractionation followed by transfer of the top (plasma) layer to a secondary non-breakable cryovials for storage at -80°C until shipment to the PK Core lab.
- Samples will be shipped with dry ice.
- Sample should be shipped (with email notification to wenb@med.umich.edu) to Pharmacokinetics Core for analysis:

Bo Wen
University of Michigan

Room 3400 of Building 520
North Campus Research Complex
1600 Huron Parkway
Ann Arbor, MI 48109.

Phone: (734) 615-3470

Email: wenb@med.umich.edu

- The time points for the PK samples are as follows ((± 15 minutes):

| Day | Timing of PK blood draw |
|----------------|---|
| C1D1 post-dose | +2 hrs |
| C2D1 pre-dose | Once anytime between 0 to -4 hrs |
| C2D1 post-dose | +0.5 hrs, +1 hr, +2 hrs, +3 hrs, +4 hrs |
| C3D1 pre-dose | Once anytime between 0 to -4 hrs |
| C3D1 post-dose | +2 hrs |

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints and Data Assessment Plan

Pazopanib with a low fat diet is a pilot study with a primary endpoint of feasibility and safety.

The primary outcome will be a description of toxicity and feasibility with the following endpoints: any hematologic toxicity of grade 4 or non-hematologic toxicities of grades 3 and 4 (excluding alopecia, and also excluding nausea and vomiting if the symptoms were manageable with standard care or antiemetic therapy); frequency and proportion of toxicities of all grades according to the CTCAE version 4.0 criteria; the frequency of dose reductions; the duration of treatment and the mean (or median) total dose taken. Each endpoint will include a 95% confidence around the reported statistic. Examples of exact confidence interval ranges with a sample size of 16 are presented in table 3.

Table 5:

| Frequency | Proportion | 95% Confidence Interval |
|-----------|------------|-------------------------|
| 1 | 6.25% | 0.2%, 30.2% |
| 2 | 12.5% | 1.6%, 38.4% |
| 3 | 18.75% | 4.1%, 45.7% |
| 6 | 37.5% | 15.2%, 64.5% |
| 8 | 50% | 24.7%, 75.4% |

The secondary objectives include overall response proportion by RECIST 1.1 including complete response and partial response at 12 weeks after start of pazopanib therapy start (CT chest, abdomen and pelvis). Each response proportion will be expressed with 95% exact binomial confidence intervals.

The pharmacokinetic data (Cmax in units of ng/mL and the trough concentration in units of micro g/mL) will be reported in context of known PK data of pazopanib administered in the fasting state⁷ and described in the context of the toxicity data.

An interim safety analysis will be conducted after 8 patients have been treated for 2 cycles on pazopanib with a low fat meal. If greater than 5 patients of the 8 experience hematologic toxicity of grade 4 or non-hematologic toxicities of grades 3 or 4 (excluding alopecia, and also excluding nausea and vomiting if the symptoms were manageable with standard care or antiemetic therapy), the study will be pause. Further study may be continued with an amendment to decrease the starting dose to 200 mg PO daily with low fat meal subject to PRC review/approval and IRB review/approval.

11.2 Sample Size and Accrual

A sample size of 16 patients with metastatic renal cell carcinoma will be enrolled over a 12 month period with an interim analysis for safety after 8 patients have completed 2 cycles. As a pilot study, this sample size is a convenience sample and sufficient to determine the feasibility of administering pazopanib with a low-fat meal in advanced renal cell carcinoma, the associated toxicity profile and preliminary efficacy measures such as ORR, PFS or overall survival.

Based on data from this pilot study, a larger follow-up study may be warranted to definitively address the cost savings of administering pazopanib with low fat meal and the efficacy of the drug when given with low fat meal.

12.0 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan. The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee, and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol to provide continuous review of the data and patient safety. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed. The report will be signed by the Principal Investigator or by one of the co-investigators. Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis for independent review.

13.0 REFERENCES

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Appendix 1. Low Fat Meal (LFM) requirements and examples:

DEFINITION: A low-fat meal contains less than ~400 calories and less than 20% fat or 10 grams per meal.

High fat containing food like bacon, sausage, etc. is not permitted with pazopanib in this study.

Examples of a low-fat breakfast include (if coffee/tea is added please use only fat free additives such as sugar or non-fat creamer or fat-free milk):

- 2 slices of wheat toast with 1 tablespoon of light margarine and 1 tablespoon of jelly, and 8 ounces of low-fat (1%) milk, 1 small apple (415 calories and 9.4 grams fat)
- ½ cup apple juice, 1/2 cup uncooked oatmeal, 1 cup low-fat (1%) milk, 1 tbsp. light margarine, 1 tbsp. raisins, 2 tsp brown sugar (420 calories and 10 grams fat).
- 2 - 4" corn tortillas, 2 tbsp. salsa, ½ ounce (1/2 slice) cheddar cheese, 2 large egg whites, 1 large egg, 1 cup fat-free (skim) milk, 1 nectarine (410 calories and 11 grams fat).
- 1 cup low-fat cottage cheese with cinnamon and topped with ½ cup diced peaches, 1 slice whole wheat toast with 1 tbsp. light margarine and 1 tbsp. jam (398 calories and 8.3 grams fat).
- 1 whole wheat bagel with 1 Tbsp. creamy peanut butter, 1 cup of fat-free milk (425 calories and 10 grams fat).
Note: can substitute 2 Tbsp. light cream cheese for the peanut butter
- Fruit Smoothie - 1 cup low-fat (1%) milk, 6 ounces of plain traditional Greek yogurt (~6 gm fat/serving), ½ cup blueberries 2 tsp. honey, 1 small banana (423 calories and 9.5 grams fat).
- 3 cups air popped popcorn with 1 tbsp. light margarine, ½ cup cinnamon applesauce, 6 ounces traditional Greek fruit-flavored yogurt (403 calories and 10.7 grams fat).
- 1 cup of cereal (such as honey nut cheerios), 8 ounces of 1% milk, 1 slice of toast with 1 tbsp. light margarine, 1 small orange (435 calories and 10.4 grams fat).
- 1 flour tortilla (2.2 oz.), 1 ounce reduced fat (2%) cheddar, ¼ cup black beans (drained), 2 tbsp. salsa, 1 pear (414 calories, 10.8 gm fat)

You can learn more or schedule a cancer nutrition services appointment by calling Cancer Nutrition Services at **877-907-0859**.

Appendix 2: Common Pazopanib Toxicities and Guidance:

| Adverse event | Supportive measure (s) |
|---|--|
| Fatigue | <ul style="list-style-type: none"> • Check for other possible contributing etiologies such as anemia • Take at night before bed with evening meal |
| Hand foot skin reaction | <ul style="list-style-type: none"> • Preventive measures: regular use of alcohol-free emollients, use of mild soaps, avoiding extreme temperatures and direct sun exposure • Avoid friction or pressure on the hands and feet, including avoiding tight-fitting footwear • Clobetasol 0.05% cream • Urea 20% cream |
| HTN | <ul style="list-style-type: none"> • Add anti-hypertensives (ACEI/ARB/CCB) • Maintain and review BP log |
| Echo heart (Transthoracic) | <ul style="list-style-type: none"> • At baseline and after 12 weeks of therapy. If LV dysfunction (<50% or <10% decline from baseline) is noted, refer to cardiology/institute CHF measures including beta blocker, ACEI/ARB etc. |
| AST/ALT elevations | <ul style="list-style-type: none"> • Please refer to table 3 of protocol |
| Diarrhea | <ul style="list-style-type: none"> • Imodium and/or lomotil as in their respective package inserts • Creon 24,000 U of lipase, 2-3/meal and 1-2/snack for a subject of 70 kg (500-2500 u/kg/meal) • Consultation with Registered Dietitian for dietary adjustments to alleviate diarrhea |
| Nausea and vomiting/ GERD/Dyspepsia/bloating/gas | <ul style="list-style-type: none"> • Anti-emetics e.g. ondansetron • Antacids (avoid proton pump inhibitors) • Simethicone and other symptomatic measures • Consultation with Registered Dietitian for dietary adjustments to alleviate diarrhea |
| Stomatitis | <ul style="list-style-type: none"> • Use of a soft toothbrush or swab • Regular rinsing with an alcohol-free mouthwash, saline solution or bicarbonate • Eating soft, room-temperature foods and avoiding hot, spicy or acidic food and drinks • Good oral hygiene |

Appendix 3:
Toxicity data Treatment-Emergent Adverse Events with frequencies observed in the pazopanib phase 3 trial²

| Adverse event | All Grades % | Grade 3 % | Grade 4 % |
|--------------------------|--------------|-----------|-----------|
| Diarrhea | 52 | 3 | < 1 |
| Hypertension | 40 | 4 | |
| Hair color changes | 38 | < 1 | |
| Nausea | 26 | < 1 | |
| Anorexia | 22 | 2 | |
| Vomiting | 21 | 2 | < 1 |
| Fatigue | 19 | 2 | |
| Asthenia | 14 | 3 | |
| Abdominal pain | 11 | 2 | |
| Headache | 10 | 0 | |
| Clinical chemistry | | | |
| ALT increase | 53 | 10 | 2 |
| AST increase | 53 | 7 | < 1 |
| Hyperglycemia | 41 | < 1 | |
| Total bilirubin increase | 36 | 3 | < 1 |
| Hypophosphatemia | 34 | 4 | |
| Hypocalcemia | 33 | 1 | 1 |
| Hyponatremia | 31 | 4 | 1 |
| Hypomagnesemia | 11 | 3 | |
| Hypoglycemia | 17 | | < 1 |
| Hematologic | | | |
| Leukopenia | 37 | | |
| Neutropenia | 34 | 1 | < 1 |
| Thrombocytopenia | 32 | < 1 | < 1 |
| Lymphocytopenia | 31 | 4 | <1 |

Appendix 4: ECOG Performance Status

| GRADE | ECOG PERFORMANCE STATUS |
|-------|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |
| 5 | Dead |

