CITY OF HOPE
1500 E. DUARTE RD.
DUARTE, CA 91010
DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: A Phase II Study of Pazopanib in VEGF-TKI Refractory Metastatic Renal Cell Carcinoma (MRCC)

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB #10030 **VERSION: 07**

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SITE: Renal Cell Carcinoma
STAGE (If applicable): **IV**
MODALITY: Oral medication
TYPE: Phase II

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A PHASE II STUDY OF PAZOPANIB IN VEGF-TKI REFRACTORY METASTATIC RENAL CELL CARCINOMA (MRCC)

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AGENT NSC# AND IND#: Pazopanib NSC#:737754; pending

COORDINATING CENTER: City of Hope Comprehensive Cancer Center

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Revised: 07.29.10; 9.15.10; 03.18.11; 10-11-11, 04-04-12, 09-26-13

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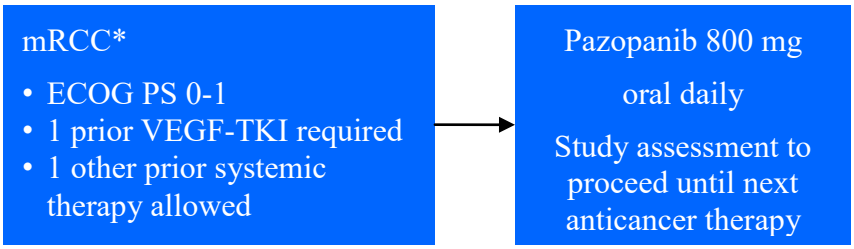
Experimental Design Schema

Open-label, phase II design as represented in the following schema:



* See inclusion/exclusion criteria for full details.

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Protocol Synopsis

Protocol Title:
A PHASE II STUDY OF PAZOPANIB IN VEGF-TKI REFRACTORY METASTATIC RENAL CELL CARCINOMA (MRCC)
Brief Protocol Title for the Lay Public (if applicable):
A PHASE II STUDY OF PAZOPANIB IN VEGF-TKI REFRACTORY METASTATIC RENAL CELL CARCINOMA (MRCC)
Study Phase:
Phase II
Participating Sites:
City of Hope Comprehensive Cancer Center
Rationale for this Study:
At present, 3rd line therapy of mRCC remains an area of need. Pazopanib has shown activity in the setting of bevacizumab- and cytokine- refractory patients.[1,2] Furthermore, there may be preclinical rationale to challenge patients with a structurally distinct VEGF-TKI. Molecular aberrations in the receptor tyrosine kinase (RTK) targeted by VEGF-TKIs may confer a relative resistance to specific agents – thus, re-challenging with agents such as sunitinib is presumably less efficacious.[3,4] Ongoing studies have assessed inhibition of distinct molecular pathways; however, response rates using this approach (i.e., with mTOR inhibitors or perifosine) have been modest at best.[5,6] 3rd- line therapy represents an area of need in metastatic renal cell carcinoma – herein, we propose use of pazopanib in this setting.
Primary Objective:
To determine the RR associated with pazopanib as 3rd-line therapy in mRCC patients who have failed therapy with a distinct VEGF-TKI
Secondary Objective(s):
• To evaluate progression-free survival (PFS), overall survival (OS) • To describe the toxicity associated with pazopanib in this patient population • To compare, within patient, time to tumor progression of 2nd-line therapy with time to tumor progression on pazopanib as 3rd-line therapy • To determine if baseline HGF, E-selectin and IL-6 are associated with PFS • To determine if pre-metastatic niche density in regional LNs is associated with PFS • To determine an association between E-selectin, IL-6 and pre-metastatic niche density • To evaluate the prognostic effect of pre-metastatic niches as an independent factor in PFS • To determine if pSTAT3 in tumor tissue is associated with PFS
Study Design:
Open-label, single institution phase II study
Primary Endpoint and Secondary Endpoints:
<u>Primary:</u>

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- RR by RECIST 1.1 Criteria

Secondary:

- Toxicity, PFS, OS

Sample Size:

28

Estimated Duration of the Study

12 months

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

- Histologically confirmed diagnosis of metastatic clear cell RCC
- At least one measurable lesion at baseline as per RECIST 1.1 criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion to be determined from the photograph
- 1 prior VEGF-TKI required
- 1 other prior systemic therapy allowed
- ECOG PS 0-1
- Resolution of grade ≥ 2 toxicity from prior therapy
- Normal hematologic labs and serum chemistries (to be specified in the protocol)
- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.
- Age ≥ 18 years or legal age of consent if greater than 18 years
- A female is eligible to enter and participate in this study if she is of non-child bearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had (1) a hysterectomy, (2) a bilateral oophorectomy (ovariectomy), (3) a bilateral tubal ligation, or (4) is post-menopausal. Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L). Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT.
- Patients with childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows: (1) 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, (2) oral contraceptive, either combined or progestogen alone, (3) injectable progestogen, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year, (4) 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, (6) double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository) Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

- Adequate organ system function as defined in Table 1

Exclusion Criteria:

- Concurrent use of other investigational agents
- Known history of allergic reactions to pazopanib or other VEGF-TKIs
- Presence of serious or uncontrolled infection
- Prior malignancy. (Note: Subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.
- Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to (1) active peptic ulcer disease, (2) known intraluminal metastatic lesion/s with risk of bleeding, (3) inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), (4) other gastrointestinal conditions with increased risk of perforation, or (5) history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to (1) malabsorption syndrome or (2) major resection of the stomach or small bowel.
- Presence of uncontrolled infection.
- Corrected QT interval (QTc) > 480 msecs using Bazett's formula
- History of any one or more of the following cardiovascular conditions within the past 6 months: (1) cardiac angioplasty or stenting, (2) myocardial infarction, (3) unstable angina, (4) coronary artery bypass graft surgery, (5) symptomatic peripheral vascular disease, or (6) Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. (Note: Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed

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on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <140/90 mmHg in order for a subject to be eligible for the study.

- History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. (Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible)
- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).
- Evidence of active bleeding or bleeding diathesis.
- Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels
- Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.
- Unable or unwilling to discontinue use of prohibited medications list as specified in the full protocol for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.
- Treatment with any of the following anti-cancer therapies: (1) radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazoapnib OR (2) chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib
- Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.
- Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is PROHIBITED beginning 14 days prior to the first dose of study drug until discontinuation from the study. Strong CYP3A4 inhibitors include (but are not limited to): certain antibiotics (including clarithromycin, telithromycin, and troleandomycin), certain HIV protease inhibitors (including ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, and lopinavir), certain ntifungals (including itraconzaole, ketoconazole, voriconazole, and fluconazole) and certain antidepressants (including nefazodone).

Investigational Product Dosage and Administration:

Pazopanib 200 mg 4 tablets oral daily

Clinical Observations and Tests to be Performed:

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Assessments within 28 Days of the First Dose Medical history:

- RCC-specific history including: date of diagnosis, primary tumor type with histology/cytology determination, current stage of cancer, prior systemic treatment(s) for RCC, ongoing toxicity related to prior treatment(s); and history of other malignancies
- Prior surgery and/or radiotherapy (date, organ/anatomic region(s) of surgery and/or radiotherapy must be documented), other significant medical and surgical histories within the past 6 months.
- Baseline bone scan for tumor assessment
- Baseline disease assessments with CT of the chest, abdomen or pelvis
- MRI or CT of the brain within 2 weeks of first dose if clinically indicated or if the subject has a history of CNS metastases

Assessments within 7 Days of the First Dose

- Physical examinations: height (only recorded at baseline) and body weight and current medical conditions.
- Vital signs: body temperature, blood pressure and heart rate. **Note:** If a subject presents with poorly controlled hypertension, defined as SBP ≥140mmHg or DBP ≥90mmHg, antihypertensive medication(s) should be initiated or adjusted with a goal to control the blood pressure to <140/90 mmHg.
- ECOG PS
- Clinical laboratory assessments, listed in 6.2
- 12-lead ECG with QTc measurement
- Baseline IL-6 and E-selectin assessment
- Serum pregnancy test for women of childbearing potential.

Pre-dose Assessments on Day 1

- Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study.
- Blood pressure measurements: subjects must have a blood pressure reading of <140/90mmHg to be eligible. If anti-hypertensives were initiated and/or dosing has been adjusted during the Baseline Period, the blood pressure must be re-assessed on two occasions consecutively that are separated by a minimum of 1 hour. The mean SBP/DBP values from both blood pressure assessments must be <140/90mmHg in order for a subject to be eligible. These two assessments must also be the most recent ones prior to randomization (the blood pressure values from the later assessment will be used as the subject's baseline blood pressure values). All the blood pressure readings must be recorded on the appropriate eCRF.
- ECOG PS: Any changes since baseline assessment should be recorded in the eCRF. Subjects having deterioration of ECOG PS to > 1 will be excluded from the study.
- Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.
- Obtain archived tumor tissue samples for biomarker assessments (if available).

Assessments on Study

- Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study. This will occur at C1D15, C2D1 and monthly thereafter (1 cycle = 28 days).
- ECOG PS: Any changes since baseline assessment should be recorded in the eCRF. Subjects having deterioration of ECOG PS to ≥2 will be excluded from the study. This will occur at C1D15, C2D1 and monthly thereafter (1 cycle = 28 days).
- Obtain blood sample for IL-6 and E-selectin measurement. This will occur monthly while patients are on study.
- Tumor assessments will be performed every 8 weeks (+/- 1 week) from randomization until the start of another anticancer therapy. A partial or complete response warrants confirmation no sooner than 4 weeks and no later than 6 weeks after its initial observation. This confirmatory scan is considered outside of standard of care, and will be funded by the sponsor.

Post-Study Assessments

- Any research participant who is discontinued from study treatment for any reason other than PD will continue to have tumor assessments every 8 weeks (+/- 1 week) until the patient starts another anticancer therapy. The investigator or his/her designee will continue collecting information on the initiation of anticancer therapies until the date of data cutoff for the final analysis. All new anticancer therapy therapies after the last dose of treatment will be recorded on the appropriate CRF.
- All research participants will be followed for survival every 6 months.

Clinical Laboratory Assessments

All clinical laboratory assessments will be performed at City of Hope. Laboratory tests should be performed at baseline, at specified visits during the study, and at the follow-up visit, all as indicated in the Time and Events Table(s). Laboratory assessments may be performed within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated.

All laboratory tests with values that become clinically abnormal while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated at the PI's discretion until the values return to normal or baseline.

Results for all unscheduled clinical laboratory assessments (i.e., hematology, TSH/T_4, coagulation parameters) should be recorded on an unscheduled laboratory form in the eCRF.

Hematology and Clinical Chemistry

Appendix A shows the hematology and clinical chemistry laboratory parameters that should be reported. Assays for hematology and clinical chemistry should be performed at baseline, every 4 weeks until 6 months, and then every 8 weeks thereafter. Hepatic assays should be performed at

baseline, 2, 4, and 8 weeks, followed by every 4 weeks until 6 months, and then every 8 weeks thereafter.

Liver Function Tests

When a separate liver function test (LFT) panel is conducted, this panel should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 x upper limit of normal (ULN). Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to ensure subject safety.

Evaluation of Proteinuria

Proteinuria will be evaluated using the urine protein to creatinine ratio (UPC; see Appendix C). UPC will be determined at times specified in the Time and Events Table. If UPC ≥ 3, then the dose modification table guidelines should be followed.

Coagulation Tests

Coagulation tests should be performed as specified in the Time and Events Table and also in response to an AE/SAE as clinically indicated. Coagulation tests include activated partial thromboplastin time (aPTT) and either prothrombin time (PT) or international normalized ratio (INR).

Lipid Tests

Lipid tests include cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. These tests should be performed as specified in the Time and Events Table. Additional testing may be performed if clinically indicated. In such a case, the subject should be in a fasting state.

Thyroid Function Tests

Thyroid function tests to assess thyroid stimulating hormone (TSH) and thyroxine (free T_4) should be performed as specified in the Time and Events Table. Unscheduled thyroid function tests (TSH and free T_4) may be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

Statistical Considerations:

The primary endpoint is the confirmed response rate (CR+PR), as determined by the RECIST 1.1

criteria. We will employ the two stage MinMax design suggested by Simon.

Prior data indicates that an overall RR of 20% can be obtained with pazopanib therapy. For patients with mRCC eligible for this 3rd line study, a response rate of 20% would represent a significant improvement over current approaches (3rd line therapy with the Akt inhibitor perifosine, for instance, yielded a 7% response rate) and would further indicate that the activity of pazopanib is maintained through multiple prior lines of therapy in selected patients.

Prior studies suggest that a response rate between 5-10% would not be an improvement over current approaches. As a result, we have set a discouraging response rate at 8%, and an encouraging response rate at 23%. Initially, we will accrue 14 patients. If there is at least 1 responder, accrual will continue to 28 patients. If 5 or more responders (18%) are observed, pazopanib will be declared promising for future studies, assuming toxicity and survival endpoints are also within acceptable limits. This Simon's MiniMax two-stage design has a type I error of 10% (probability of declaring an agent with a true 8% response rate as promising), and a power of 80% (probability of *not* declaring an agent promising with a true 23% response rate is 10%). All eligible patients treated will be included in the calculation of response rate. Any patients with an unknown response rate will be included as a non-responder.

This design has 31% chance of stopping at the first stage if true response rate is 8%.

Toxicity will be monitored on an ongoing basis. If the number of unacceptable toxicities exceeds 1 in the first 3, or exceeds 2 in the first 6 or more than 25% thereafter, the study will hold accrual for an amendment regarding treatment modifications or study termination. Toxicity will be graded and recorded for each patient in this population according to CTCAE 4.0.

Secondary endpoints include progression-free survival (PFS), overall survival (OS), and toxicity, and we will also compare PFS on this study to time to progression on the previous line of therapy.

Additional secondary endpoints relate to biological correlates, including E-Selection, IL-6, the pre-metastatic niche density, pSTAT3, and baseline HGF. Because the nature of these secondary endpoints is exploratory, we will not consider the issue of multiple comparisons and the according adjustment of p-values.

Univariate or multivariate Cox proportional hazards model will be invoked to assess the association of these biological correlatives and both PFS and OS.

In addition, a t-test will be conducted to determine if there is an association between E-selectin, IL-6 and the pre-metastatic niche density.

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Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

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1.0 Goals and Objectives (Scientific Aims)

1.1 Primary Objectives

1.1.1 To determine the RR associated with pazopanib as 3rd-line therapy in mRCC patients who have failed therapy with a distinct VEGF-TKI

1.2 Secondary Objectives

1.2.1 To determine if baseline HGF, E-selectin and IL-6 are associated with PFS

1.2.2 To determine if pre-metastatic niche density in regional LNs is associated with PFS

1.2.3 To determine an association between E-selectin, IL-6 and pre-metastatic niche density

1.2.4 To evaluate the prognostic effect of pre-metastatic niches as an independent factor in time to first relapse

1.2.5 To determine if pSTAT3 in tumor tissue is associated with PFS

1.2.6 To describe the toxicity associated with pazopanib in this patient population

1.2.7 To evaluate PFS and OS

1.2.8 To compare, within patient, time to tumor progression of 2nd-line therapy with time to tumor progression on pazopanib as 3rd-line therapy

2.0 Background

2.1 Current Standards: 1st-Line Therapy for mRCC

Today, the oncologist is armed with a multitude of active agents for the therapy of metastatic renal cell carcinoma (mRCC). An enhanced understanding of pathways related to RCC tumorigenesis has led to the development of clinically validated targeted therapies. At present, these agents can be broadly divided into two classes, inhibitors of vascular-endothelial growth factor (VEGF)-mediated signaling and inhibitors of the mammalian target of rapamycin (mTOR). Substantial evidence exists to support use of the former class of agents as 1st-line therapy for mRCC. VEGF-mediated signaling may be abrogated by inhibition of the intracellular tyrosine kinase domain of the VEGF-receptor with agents such as sunitinib, or by neutralization of circulating VEGF with agents such as bevacizumab. In a randomized, phase III trial including 750 previously untreated patients with metastatic clear cell RCC, sunitinib was shown to improve overall survival (OS) as compared to IFN-□ (26.4 mos *vs* 21.8 mos, P=0.051).[7] With censoring of patients who crossed over to sunitinib therapy, this difference was even more pronounced (26.4 mos *vs* 20.0 months, P=0.036). Data for bevacizumab derived from two phase III trials (AVOREN and CALGB 90206) suggests substantial activity as first-line therapy for mRCC in combination with IFN-□; however, survival data with bevacizumab fails to surpass the "highwater mark" achieved with sunitinib.[8-10]

Within the past several months, a distinct VEGF-TKI has gained FDA approval for the treatment of mRCC. The novel TKI pazopanib demonstrates strong affinity for VEGFR-2 (inhibiting the moiety at serum concentrations of 17.5 mcg/mL), and was recently examined in a pivotal phase III trial.[11] In this study, 400 patients with clear cell mRCC and either no prior therapy or 1 prior cytokine-based therapy were randomized in a 2:1 fashion to receive pazopanib at 800 mg oral daily or placebo. The study met its prior endpoint of improved PFS (9.2 *vs* 4.2 mos, P<0.0000001), and showed an even more impressive difference in PFS amongst treatment-naïve patients enrolled (11.1 *vs* 2.8 mos, P<0.0000001). The agent

was well tolerated, with diarrhea, hypertension and hair color change representing the most frequent treatment-related adverse events. Already, the agent has been allotted a category 1 recommendation (along with bevacizumab/IFN and sunitinib) in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.[12]

2.2 Current Standards: 2nd-Line Therapy for mRCC

Subsequent to failure of a VEGF-TKI, there is a role for therapy with the mTOR inhibitor everolimus. A phase III experience with this agent has been reported, randomizing 416 patients who had previously progressed on VEGFR-tyrosine kinase inhibitor (TKI) therapy to either everolimus or placebo.[5] Results from a second interim analysis of this trial demonstrate a substantial increase in PFS with everolimus therapy (4.9 mos *v* 1.9 mos, P<0.001). OS associated with everolimus therapy was 14.8 months; taken together with data from the phase III experience with sunitinib, OS for patients with advanced RCC can now be projected at upwards of 41 mos with initial sunitinib therapy followed by everolimus.

2.3 Beyond 2nd-Line Therapy for mRCC

Trials are currently ongoing to determine the optimal sequencing of therapy in mRCC. As one example, RECORD-3 will compare 1st-line therapy with either sunitinib or everolimus, followed by crossover to the other agent at the time of progression.[13] Though such efforts will optimize 1st- and 2nd-line therapy, there is currently a need for trials exploring approaches beyond failure of antiangiogenesis and mTOR inhibitors in mRCC. At present, observational studies suggest that oncologists frequently re-challenge patients with a VEGF-TKI after initial failure.[14] Although somewhat counter-intuitive, data from these series suggest that (in the 2nd line setting) patients may have a higher response rate to re-challenge with a VEGF-TKI as compared to an initial challenge with an mTOR inhibitor. A retrospective analysis of patients given consecutive treatment with sorafenib followed by sunitinib demonstrated response rates of up to 17% with sunitinib therapy.[15] Impressively, in a similar analysis of patients receiving a reversed schedule of these agents, one patient treated with sunitinib followed by sorafenib exhibited a complete response.

2.4 Rationale for Pazopanib as 3rd-Line Therapy

Though the approach of re-challenging mRCC patients with VEGF-TKI therapy appears to be reasonably efficacious in retrospective series, clearly this strategy warrants further prospective validation (the ongoing AXIS and SWITCH studies may define the feasibility of this approach).[16-18] Pazopanib has shown activity in the setting of bevacizumab- and cytokine- refractory patients.[1,2] Furthermore, there may be preclinical rationale to challenge patients with a structurally distinct VEGF-TKI. Molecular aberrations in the receptor tyrosine kinase (RTK) targeted by VEGF-TKIs may confer a relative resistance to specific agents – thus, re-challenging with agents such as sunitinib is presumably less efficacious.[3,4] Ongoing studies have assessed inhibition of distinct molecular pathways; however, response rates using this approach (i.e., with mTOR inhibitors or perifosine) have been modest at best.[5,6] 3rd- line therapy represents an area of need in metastatic renal cell carcinoma – herein, we propose use of pazopanib in this setting.

2.5 Cytokine and Angiogenic Factors (CAFs): Potential Predictors of Response?

Responses observed with pazopanib therapy may be augmented by appropriate selection of patients with sensitivity to the agent. Data from a randomized discontinuation trial of pazopanib have recently been reported.[19] In this study, 225 patients with mRCC (both treatment-naïve and refractory) were treated with 12 weeks of pazopanib at the approved dose of 800 mg oral daily. Patients were continued on therapy thereafter if a CR or PR was obtained, and discontinued if PD was observed. Initially, patients with SD

were randomized to either pazopanib or placebo; however, in light of robust clinical activity, this randomization was ultimately halted. On independent review, pazopanib was associated with a clinical benefit rate (CBR; CBR = CR + PR) of 34.7%, and a median OS of 11.9 mos.

Correlative analyses to accompany this study included comprehensive assessment of CAFs obtained at baseline and during therapy.[20] Elevated levels of HGF, IL-6 and IL-8 were significantly correlated with less tumor shrinkage in patients treated with pazopanib. Lower IL-6 baseline levels of IL-6 were associated with a profound improvement in PFS (77.7 *v* 28.6 wks). Notably, other studies have suggested the predictive and prognostic relevance of IL-6 in the setting of distinct therapies.[21,22] While the data presented herein is encouraging, prospective validation is necessary to determine the true clinical utility of IL-6 as a predictive marker with pazopanib therapy.

2.6 IL-6/STAT3: Role in RCC Tumorigenesis

IL-6 may play a role in RCC tumorigenesis through activation of STAT3-related pathways.[23] Seminal observations by Yu and Figlin indicate that inhibition of STAT3 activation by VEGF-TKIs correlates with their apoptotic effect.[24] This may occur through a multitude of mechanisms, including immune modulation. *In vivo* experiments suggest that VEGF-TKI therapy leads to decreased STAT3 activation in tumor-associated myeloid-derived suppressor cells (MDSCs), and further decreases the quantity of tumor MDSCs and tumor T-regulatory cells.

In the current proposal, the role of IL-6 as a predictive marker is examined in the context of 3rd-line therapy with pazopanib. Given that 3rd-line therapy for mRCC represents an area of need and that the majority of patients will have already encountered previous treatment with a VEGF-TKI, use of relevant biomarkers to select appropriate patients is paramount. Correlative studies assessing the role of STAT3 may validate the purported role of IL-6 in RCC tumorgenesis.

2.7 Other Biomarkers of Pazopanib Response Identified in the Randomized Discontinuation Study

Outside of IL-6 level, data from the randomized discontinuation study of pazopanib previously cited provided hypothesis-generating data regarding the prognostic role of E-selectin. Specifically, using a two-factor signature with E-selectin and IL-6, selected groups with significantly different PFS could be identified. Patients with low IL-6 and high E-selectin had superior PFS (median: 100 wks) in comparison to those patients with high IL-6 and low E-selectin (median: 28.3 wks). An intermediate group of patients comprised of patients with high or low levels of both IL-6 and E-selectin had a median PFS of 53.0 wks.

2.8 Unifying E-Selectin and IL-6: The Pre-Metastatic Niche

A "seed-and-soil" hypothesis has been *en vogue* as an explanation for metastatic progression in multiple malignancies.[25] Recently, strong preclinical rationale has emerged for this hypothesis, suggesting that bone marrow derived cells (BMDCs) are stimulated to migrate to 'pre-metastatic' sites by various inflammatory cytokines, including IL-6.[26,27] As outline on the following page, the pre-metastatic niche is cultivated into an area conducive to tumor migration through various molecular mediators which modify the extracellular matrix. Strong evidence implicates the role of E-selectin, VEGFA and LOX, amongst other moieties, in this process.[28,29]

Given the role of both IL-6 and E-selectin in this model, the currently proposed study offers a prime opportunity to explore whether the pre-metastatic niche can explain their prognostic role. In the setting of mRCC, the nice can be assessed in regional lymph nodes (LNs) harvested at the time of nephrectomy.

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Pre-metastatic niche density (characterized as the number of clusters of $VEGFR1^{+}VLA\text{-}4^{+}$ cells per x 100 objective field) can be used as a quantitative assessment.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Histologically confirmed diagnosis of metastatic clear cell RCC

3.1.2 At least one measurable lesion at baseline as per RECIST 1.1 criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion to be determined from the photograph

3.1.3 1 prior VEGF-TKI required

3.1.4 1 other prior systemic therapy allowed

3.1.5 ECOG PS 0-1

3.1.6 Resolution of grade ≥ 2 toxicity from prior therapy

3.1.7 Normal hematologic labs and serum chemistries (see table 1, under 3.1.12 for definition of normal)

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

3.1.9 Age ≥ 18 years or legal age of consent if greater than 18 years

3.1.10 A female is eligible to enter and participate in this study if she is of non-child bearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had (1) a hysterectomy, (2) a bilateral oophorectomy (ovariectomy), (3) a bilateral tubal ligation, or (4) is post-menopausal. Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L). Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT.

3.1.11 Patients with childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows: (1) complete

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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, (2) oral contraceptive, either combined or progestogen alone, (3) injectable progestogen, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year, (4) 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, (6) double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository) Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

3.1.12 Adequate organ system function as defined in Table 1

Table 1. Definitions for Adequate Organ Function

System	Laboratory Values
Absolute neutrophil count (ANC)	≥1.5 X 109/L
Hemoglobin	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 109/L
Prothrombin time (PT) or international normalized ratio (INR)[a]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[b]	≤2.5 X ULN
Serum creatinine	≤2.0 mg/dL (133 µmol/L)
Or, if >2.0 mg/dL: Calculated creatinine clearance (ClCR) by Cockroft-Gault formula	≥30 mL/min
Urine Protein to Creatinine Ratio (UPC; appropriate appendix)[c]	<1

a. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
b. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
c. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

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3.2 Exclusion Criteria

3.2.1 Concurrent use of other investigational agents

3.2.2 Known history of allergic reactions to pazopanib or other VEGF-TKIs

3.2.3 Presence of serious or uncontrolled infection

3.2.4 Prior malignancy. (Note: Subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.

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

3.2.6 Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to (1) active peptic ulcer disease, (2) known intraluminal metastatic lesion/s with risk of bleeding, (3) inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), (4) other gastrointestinal conditions with increased risk of perforation, or (5) history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.

3.2.7 Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to (1) malabsorption syndrome or (2) major resection of the stomach or small bowel.

3.2.8 Corrected QT interval (QTc) > 480 msecs using Bazett's formula

3.2.9 History of any one or more of the following cardiovascular conditions within the past 6 months: (1) cardiac angioplasty or stenting, (2) myocardial infarction, (3) unstable angina, (4) coronary artery bypass graft surgery, (5) symptomatic peripheral vascular disease, or (6) Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)

3.2.10 Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. (Note: Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <140/90 mmHg in order for a subject to be eligible for the study.

3.2.11 History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. (Note:

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

3.2.12 Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

3.2.13 Evidence of active bleeding or bleeding diathesis.

3.2.14 Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels

3.2.15 Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks prior to the first dose of study drug.

3.2.16 Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.

3.2.17 Unable or unwilling to discontinue use of prohibited medications list as specified in the full protocol for at least 14 days of a drug prior to the first dose of study drug and for the duration of the study.

3.2.18 Treatment with any of the following anti-cancer therapies: (1) radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazoapnib OR (2) chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib

3.2.19 Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.

3.2.20 Non-Compliance: Patients, who in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

3.2.21 Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is PROHIBITED beginning 14 days prior to the first dose of study drug until discontinuation from the study. Strong CYP3A4 inhibitors include (but are not limited to): certain antibiotics (including clarithromycin, telithromycin, and troleandomycin), certain HIV protease inhibitors (including ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, and lopinavir), certain ntifungals (including itraconzaole, ketoconazole, voriconazole, and fluconazole) and certain antidepressants (including nefazodone).

3.3 Inclusion of Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in this trial which will accrue approximately 28 patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

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4.0 Screening and Registration Procedures

4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient's research chart and medical record. Studies or procedures that were performed for clinical indications (not exclusively to determine study eligibility) and within the screening window, may be used for baseline values even if the studies were done before informed consent was obtained.

4.1.1 Assessments within 28 days of the first dose

4.1.1.1 Medical history:

4.1.1.2 Renal cell carcinoma specific history including: date of diagnosis, primary tumor type with histology/cytology determination, current stage of cancer, prior systemic treatment(s) for RCC, ongoing toxicity related to prior treatment(s); and history of other malignancies

4.1.1.3 Prior surgery and/or radiotherapy (date, organ/anatomic region(s) of surgery and/or radiotherapy must be documented), other significant medical and surgical histories within the past 6 months.

4.1.1.4 Baseline bone scan for tumor assessment

4.1.1.5 Baseline disease assessments of chest, abdomen and pelvis using CT or MRI

4.1.1.6 MRI or CT of the brain within 2 weeks of first dose if clinically indicated or if the subject has a history of CNS metastases

4.1.2 Assessments within 7 days of the first dose

4.1.2.1 Physical examinations: height (only recorded at baseline) and body weight and current medical conditions.

4.1.2.2 Vital signs: body temperature, blood pressure and heart rate.

Note: If a subject presents with poorly controlled hypertension, defined as SBP ≥140mmHg or DBP ≥90mmHg, antihypertensive medication(s) should be initiated or adjusted with a goal to control the blood pressure to <140/90 mmHg.

4.1.2.3 ECOG PS

4.1.2.4 Clinical laboratory assessments.

4.1.2.5 12-lead ECG with QTc measurement

4.1.2.6 Baseline IL-6 and E-selectin assessment

4.1.2.7 Serum pregnancy test for women of childbearing potential.

4.1.3 Pre-dose Assessments on Day 1

4.1.3.1 Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study.

4.1.3.2 Blood pressure measurements: subjects must have a blood pressure reading of <140/90mmHg to be eligible.

4.1.3.3 ECOG PS: Any changes since baseline assessment should be recorded in the eCRF. Subjects having deterioration of ECOG PS to ≥2 will be excluded from the study

4.1.3.4 Review results of all the other baseline assessments to determine the subject's eligibility for the study. Any screening laboratory results outside the normal range will be repeated (prior to the first dose) at the discretion of the Investigator. All laboratory results must be within the values outlined in the Inclusion Criteria before the first dose of study drug.

4.1.3.5 Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.

4.1.3.6 Obtain archived tumor tissue samples for biomarker assessments (if available).

4.1.3.7 Obtain a blood sample for biomarker research. It is preferable to collect the sample on the first day of dosing but the sample may be collected at any time after first dose of investigational product. **Note**: a signed written informed consent for participating biomarker research must be obtained before collecting the blood sample for biomarker analysis.

5.0 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient and a signed informed consent will be obtained.

5.1 Registration Requirements/Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the PI or collaborating investigator, a patient will be entered on study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the PI, FAX a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form.

The nurse or data manager must log into the Electronic Data Capture (EDC) system and enter the eligibility/registration data for their reserved patient. The research nurse or data manager at the participating site will then:

- Verify eligibility
- Register the patient on study
- Assign a patient accession number

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- Confirm the patient study number and dose level in the EDC system

6.0 Treatment Program

6.1 Treatment Overview

Treatment will be administered in an outpatient setting.

6.1.1 Schedule

Pazopanib should be taken at a dose of 800 mg oral daily, with 28 days of therapy constituting 1 cycle.

6.1.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days (+/- 3 days) if the patient has at least stable disease and continue to meet laboratory parameters as defined in the eligibility section.

6.2 Laboratory Studies

A local laboratory is to be used to perform all clinical laboratory assessments. Laboratory tests should be performed at baseline, at specified visits during the study, and at the follow-up visit, all as indicated in the Time and Events Table(s). Laboratory assessments may be performed within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated.

All laboratory tests with values that become clinically abnormal while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline.

Results for all unscheduled clinical laboratory assessments (i.e., haematology, TSH/T_4, coagulation parameters) should be recorded on an unscheduled laboratory form in the eCRF.

Hematology and Clinical Chemistry

Appendix A shows the hematology and clinical chemistry laboratory parameters that should be reported. Assays for hematology and clinical chemistry should be performed at baseline, every 4 weeks until 6 months, and then every 8 weeks thereafter. Hepatic assays should be performed at baseline, 2, 4, and 8 weeks, followed by every 4 weeks until 6 months, and then every 8 weeks thereafter.

Estimated creatinine clearance should be calculated using the Cockroft and Gault method.

Liver Function Tests

When a separate liver function test (LFT) panel is conducted, this panel should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 x upper limit of normal (ULN). Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to ensure subject safety.

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Evaluation of Proteinuria

Proteinuria will be evaluated using the urine protein to creatinine ratio (UPC; see Appendix C). UPC will be determined at times specified in the Time and Events Table. If UPC ≥ 3, then the dose modification table guidelines should be followed.

Coagulation Tests

Coagulation tests should be performed as specified in the Time and Events Table and also in response to an AE/SAE as clinically indicated. Coagulation tests include activated partial thromboplastin time (aPTT) and either prothrombin time (PT) or international normalized ratio (INR).

Lipid Tests

Lipid tests include cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. These tests should be performed as specified in the Time and Events Table. Additional testing may be performed if clinically indicated. In such a case, the subject should be in a fasting state.

Thyroid Function Tests

Thyroid function tests to assess thyroid stimulating hormone (TSH) and thyroxine (free T_4) should be performed as specified in the Time and Events Table. Unscheduled thyroid function tests (TSH and free T_4) may be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

6.3 Studies Obtained During the Trial

Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study. This will occur at C1D15, C2D1 and monthly thereafter (1 cycle = 28 days).

ECOG PS: Any changes since baseline assessment should be recorded in the eCRF. Subjects having deterioration of ECOG PS to ≥2 will be excluded from the study. This will occur at C1D15, C2D1 and monthly thereafter (1 cycle = 28 days).

Obtain blood sample for IL-6 and E-selectin measurement. This will occur monthly while patients are on study.

Tumor assessments will be performed every 8 weeks (+/- 1 week) from randomization until the start of another anticancer therapy. A partial or complete response warrants confirmation no sooner than 4 weeks and no later than 6 weeks after its initial observation.

6.4 Post-Study Assessments

Any patient who is discontinued from study treatment for any reason will continue to have tumor assessments every 12 weeks (+/- 1 week) until the patient starts another anticancer therapy. The investigator or his/her designee will continue collecting information on the initiation of anticancer therapies until the date of data cutoff for the final analysis. All new anticancer therapy therapies after the last dose of treatment will be recorded on the appropriate CRF.

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6.5 Criteria for Removal from Study

Treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
- Treatment delays of > 2 weeks due to adverse events.

Treatment may be interrupted within a cycle for up to 2 weeks and missed doses should be omitted. However, patients will be replaced if they do not receive at least 80% of the planned treatment in the first cycle of therapy.

6.6 Supportive Care and Other Concomitant Therapy

6.6.1 Investigational Therapy

No other investigational treatment may be given while the patient is on study.

6.6.2 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

6.6.3 Concomitant Medications

Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the case report form (CRF) with indication, dose information, and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Permitted Medications – Use with Caution

Specific recommendations regarding anticoagulants:

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Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

Specific recommendations regarding hypoglycemic therapy including insulin:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib (British Journal of Cancer 2008: 99, 1380). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

The Effects of Pazopanib on Other Drugs

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is an inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, 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. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)

- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)

- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)

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- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)

- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

The Effects of Other Drugs on Pazopanib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section on Prohibited Medications); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. **Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to)**:

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)

- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine

- HIV antivirals: efavirenz, nevirapine

- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene

- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Prohibited Medications

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study. **Strong CYP3A4 inhibitors include (but are not limited to)**:

- Antibiotics: clarithromycin, telithromycin, troleandomycin

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- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone

6.6.4 Other Treatments Allowed on Study

Surgery and radiation therapy are not permitted while the patient is on the current study.

7.0 Dose Delays/Modifications for Adverse Events

Recommendations for investigational product (IP) dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following sections.

As a general rule, if dose reduction of IP is necessary, the dose should be reduced stepwise by 200 mg at each step, and the subject should be monitored for 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the IP 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 IP dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

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

7.1 Dose Interruptions/Modifications for Specific, Non-liver Related, Toxicities

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 1

Table 1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of	Step 1. Continue investigational product (IP) at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s).

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AE Terms & Descriptions	Dose Modification Algorithms
≥20 mmHg.	Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a cardiologist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting IP, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a cardiologist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg if IP was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt IP Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a cardiologist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue IP and continue follow-up per protocol.
Proteinuria	
UPC ≥ 3 grams	Step 1. Interrupt IP. Step 2. Test weekly the UPC until the level is < 3 grams.

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AE Terms & Descriptions	Dose Modification Algorithms
	Then, restart IP dose reduced by 200 mg. Step 3. If UPC ≥ 3 grams recurs, repeat Steps 1 and 2. Step 4. If UPC ≥ 3 grams recurs and the IP dose can no longer be reduced, discontinue IP and continue follow up per protocol.
Haemorrhage /Bleeding	
Grade 1	Continue IP with current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue IP and continue follow-up per protocol. Otherwise, interrupt IP until the AE resolved to ≤ Grade 1. Step 2. Restart IP; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue IP and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue IP with same dose; initiate and monitor anticoagulation as clinically indicated.
Grade 3	Step 1. Interrupt IP. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume IP at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one

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AE Terms & Descriptions	Dose Modification Algorithms
	week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in IP dosing (eg, re-initiating, escalating/de-escalating, or discontinuing IP), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue IP and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue IP and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue IP with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 2. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IP and follow-up per protocol
Anaemia: No specific dose reduction rules are indicated for anaemia unless due to haemorrhage or bleeding as noted above.	
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue IP; monitor as clinically indicated.

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AE Terms & Descriptions	Dose Modification Algorithms
Grade 2 or 3, if clinically significant	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 1. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue IP and continue follow-up per protocol.
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	Continue IP; monitor as clinically indicated.
QTc ≥500 msec	Discontinue IP and continue follow-up per protocol.

a. Well-controlled BP defined as mean SBP <140 mmHg and mean DBP <90 mmHg.

b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events 4.0 (NCI CTCAE 4.0).

Abbreviations: BP, blood pressure; IP, investigational product.

7.2 Dose Interruptions/Modifications for Hepatotoxicity

Recommendations for investigational product dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 3. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications, and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary.

Table 3. Dose modifications for hepatotoxicity.

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x upper limit of normal (ULN)	Continue IP at current dose with full panel liver function tests (LFTs)[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	1. Continue IP at current dose. 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: • Eosinophil count • Viral serology for hepatitis A, B and C • Liver imaging 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine

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Event	Dose Modification Algorithms
	aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1.
(C). ALT >8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence** 1. Interrupt IP until toxicity resolves to ≤ Grade 1 or baseline 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: • Eosinophil count • Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus IgM antibody, or heterophile antibody, or monospot testing) • Liver imaging 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1. 4. If the subject is benefiting from the study treatment, contact GSK Study Physician for possible re-challenge. Re-treatment may be considered if ALL following criteria are met: • ALT/AST reduced to Grade 1 • Total bilirubin <1.5 x ULN or direct bilirubin ≤35% • No hypersensitivity signs or symptoms • Subject is benefiting from therapy. If approval for retreatment is granted, the subject must be reconsented (with new informed consent specific to hepatotoxicity). **Recurrence** Discontinue IP permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated.
(D). ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash).	1. Discontinue IP immediately 2. Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: • Eosinophil count • Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus IgM antibody, or heterophile antibody, or monospot testing) • Anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody • Serum creatinine phosphokinase for possible muscle injury caused LFT elevation • Liver imaging (ultrasound or CT scan) 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until LFTs reduced to Grade 1.
For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT < 3 X ULN)	1. Isolated hyperbilirubinemia (ie in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. 2. If bilirubin is > 2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is

Event	Dose Modification Algorithms
	predominantly indirect (unconjugated), continue pazopanib at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT and total bilirubin.

8.0 Data Safety and Monitoring

8.1 Definition of Risk Level

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving COH as IND holder in a Phase II Trial.

8.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, collaborating investigator, CRA/protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS

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4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted quarterly from the anniversary date of activation. Protocol specific data collection will include the following items: Adverse event reporting and quarterly safety assessment of pazopanib.

8.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

- *Serious Adverse Event (SAE) **[21 CFR 312.32] is defined as*** **any expected or unexpected adverse event** ***that results in any of the following outcomes:***
  - Death
  - Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
  - Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect
  - Secondary Malignancy

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- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

8.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

- *Serious Adverse Events* - ***All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).***

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

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Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

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Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

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Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

ADDITIONAL REPORTING REQUIREMENTS

SAEs meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting which can found at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

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All serious adverse events must be reported by facsimile within 24 hours to the study's PI (Sumanta Kumar Pal, MD) and GlaxoSmithKline. MDC - Oncology Fax: (610) 675-2632

For medical emergencies contact:

Julie Maltzman, MD: (610) 917-4079

Toll Free Number: (800) 877-7074, ext. 4079

After Hours or Weekends: (800) 366-8900, ask for physician on call

GlaxoSmithKline UP4420

1250 S. Collegeville Road,

P.O. Box 5089

Collegeville, PA 19426-0989

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to the study PI (Sumanta Kumar Pal, MD) and GSK within 24 hours. Fax number for reporting of SAE: (610) 675 2632

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

8.1 Regulatory Reporting Requirements for Agent(s) under an IND

Serious adverse events that are unexpected and relationship to the study investigational agent cannot be ruled out, must be conveyed to the study PI (Sumanta Kumar Pal, M.D.) within 24 hours of receipt of notification of event. A Mandatory MedWatch Reporting Form (Form **FDA 3500A**) for recording information related to such an event must be included in the iRIS report.

9.0 Agent Information

9.1 Pazopanib (Votrient; GW786034)

NSC#: 737754

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9.1.1 Structure and Molecular Weight:

$C_{21}H_{23}N_7O_2S$-HCl, MW 474.0 (monohydrate salt)

9.1.2 Supplier

Glaxo-Smith-Kline

9.1.3 Formulation

Pazopanib monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200mg and 400mg of the freebase:

- 200mg, oval-shaped, white, packaged in bottles containing 34 tablets each

Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.

9.1.4 Storage

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

9.1.5 Stability

Stability studies are ongoing.

9.1.6 Administration

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. If a dose is missed, the subject should take the dose as soon as possible, but not if there are less than 12 hours 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 another dose is not permitted on that day. The subject should resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

9.1.7 Human Toxicities

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 1019 patients.* Below is the CAEPR for pazopanib (GW786034).

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Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 1019]			***EXPECTED AEs FOR ADEERS REPORTING*** **Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD/BONE MARROW			***Expected***
	Leukocytes (total WBC)		***Leukocytes (total WBC)***
	Lymphopenia		***Lymphopenia***
	Neutrophils/granulocytes (ANC/AGC)		***Neutrophils/granulocytes (ANC/AGC)***
	Platelets		***Platelets***
CARDIAC ARRHYTHMIA			
		Prolonged QTc interval (accompanied by Torsades de pointes)	
CARDIAC GENERAL			
		Cardiac ischemia/infarction	
Hypertension			***Hypertension***
		Left ventricular systolic dysfunction	
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			***Fatigue (asthenia, lethargy, malaise)***
	Weight Loss		
DERMATOLOGY/SKIN			
	Hair loss/alopecia (scalp or body)		***Hair loss/alopecia (scalp or body)***
Hypopigmentation			***Hypopigmentation***
	Rash/desquamation		***Rash/desquamation***
		Rash: hand-foot skin reaction	
ENDOCRINE			
	Thyroid function, low (hypothyroidism)		
GASTROINTESTINAL			
Anorexia			***Anorexia***
	Constipation		
	Dehydration		***Dehydration***
Diarrhea			***Diarrhea***
		Fistula, GI – Select	***Fistula, GI - Select***

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Nausea			***Nausea***
		Perforation, GI - Select	***Perforation, GI - Select***
	Taste alteration (dysgeusia)		
Vomiting			***Vomiting***
HEMORRHAGE/BLEEDING			
		Hemorrhage, GI - Select	
	Hemorrhage, pulmonary/ upper respiratory - Select		***Hemorrhage, pulmonary/upper respiratory - Select***
METABOLIC/LABORATORY			
	ALT, SGPT (serum glutamic pyruvic transaminase)		***ALT, SGPT (serum glutamic pyruvic transaminase)***
	AST, SGOT(serum glutamic oxaloacetic transaminase)		***AST, SGOT(serum glutamic oxaloacetic transaminase)***
	Amylase		
	Bilirubin (hyperbilirubinemia)		***Bilirubin (hyperbilirubinemia)***
	Glucose, serum-high (hyperglycemia)		***Glucose, serum-high (hyperglycemia)***
	Glucose, serum-low (hypoglycemia)		***Glucose, serum-low (hypoglycemia)***
	Lipase		
	Magnesium, serum-high (hypermagnesemia)		
	Magnesium, serum-low (hypomagnesemia)		
	Phosphate, serum-low (hypophosphatemia)		***Phosphate, serum-low (hypophosphatemia)***
	Proteinuria		***Proteinuria***
NEUROLOGY			
	Dizziness		***Dizziness***
	Extrapyramidal/involuntar y movement/restlessness		
PAIN			
	Pain - Abdomen NOS		***Pain - Abdomen NOS***
	Pain - Head/headache		***Pain - Head/headache***
	Pain - Joint		***Pain - Joint***
	Pain - Muscle		
	Pain - Tumor pain		
PULMONARY/UPPER RESPIRATORY			
	Cough		
	Dyspnea		
RENAL/GENITOURINARY			
		Fistula, GU – Select	***Fistula, GU - Select***

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Also reported on pazopanib (GW786034) trials but with the relationship to pazopanib (GW786034) still undetermined:

BLOOD/BONE MARROW - Hemoglobin

CARDIAC ARRHYTHMIA - Supraventricular and nodal arrhythmia - Atrial fibrillation; Supraventricular and nodal arrhythmia - Sinus bradycardia

COAGULATION - INR (International Normalized Ratio of prothrombin time); PTT (Partial Thromboplastin Time)

CONSTITUTIONAL SYMPTOMS - Fever

DERMATOLOGY/SKIN - Pruritus/itching

GASTROINTESTINAL - Dysphagia (difficulty swallowing); Flatulence; Heartburn/dyspepsia; Obstruction, GI - Small bowel NOS

HEMORRHAGE/BLEEDING - Hemorrhage, CNS; Hemorrhage, GU - Urinary NOS

HEPATOBILIARY - Pancreatitis

METABOLIC/LABORATORY - Alkaline phosphatase; Calcium, serum-low (Hypocalcemia); Creatinine; Potassium, serum-high (Hyperkalemia); Potassium, serum-low (Hyperkalemia); Sodium, serum-high (Hypernatremia); Sodium, serum-low (Hyponatremia)

MUSCULOSKELETAL/SOFT TISSUE - Muscle weakness, generalized or specific area (not due to neuropathy) - Whole body/generalized

NEUROLOGY - Confusion

OCULAR/VISUAL - Vision, blurred vision

PAIN - Pain - Back; Pain - Chest/thorax NOS; Pain - Pleura; Pain - Throat/pharynx/larynx

PULMONARY/UPPER RESPIRATORY - Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis

VASCULAR - Thrombosis/thrombus/embolism

Note: Pazopanib (GW786034) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent

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9.2 Agent Ordering

A drug supply request form is included in Appendix A.

10.0 Correlative/Special Studies

10.1 Laboratory Correlative Studies Measurement of HGF, E-selectin and IL-6

Patients will have a baseline assessment of IL-6 and E-selectin using previously described techniques.[20] Serum samples (within 2 weeks of collection) will be inserted into the Cyto-8 MAX BIOCHIP and serum IL-6 and E-selectin will be measured using SearchLight, an automated, multiplex immunoassay workstation from Aushon Biosystem. A total of 7.5 mL of blood will be collected in CPT tubes along with baseline laboratories. Plasma will be separated and stored at -80^{o}C in the laboratory of Dr. Hua Yu.

10.1.2 Measurement of pre-metastatic niche density and pSTAT3

If patient consent is obtained, a total of 12 unstained slides derived from tumor and 12 unstained slides derived from normal lymph node tissue will be requested. Normal lymph node tissue will be assessed for pre-metastatic niche density, characterized as the number of clusters of VEGFR1^{+}VLA-4^{+} cells per x 100 objective field.[29] This assessment will be performed through previously defined techniques.

pSTAT3 will be measured in paraffin-embedded sections. The authors of the protocol understand that collection procedures for specimens in this retrospective analysis are not standardized, and this may lead to inherent variability in pSTAT3 levels. Acknowledging this potential caveat, we would like to measure pSTAT3 and determine the relationship of this activated moiety to PFS. pSTAT3 will be determine through previously reported techniques.[24]

11.0 Study Calendar

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12[c]	Off Study[d]
Pazopanib 800 mg oral daily[a]		X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X		X		X				X				X
Vital signs	X	X		X		X				X				X
Height	X													
Weight	X	X		X		X				X				X
Performance Status	X	X		X		X				X				X
CBC w/diff, plts	X	X		X		X				X				X
Serum chemistry[b]	X	X		X		X				X				X
EKG	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks, ± 1 week. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[d]
Radiologic evaluation	X	Radiologic measurements should be performed every 8weeks.												X[d]
B-HCG (women of child-bearing potential)	X													
Collection of IL-6, E-selectin	X					X				X				X
UPC	X	X				X				X				X[d]
Collection of tumor specimens	X													

a: Excepting adjustments for toxicity. b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium. c: After week 12, on study, continue daily oral pazopanib therapy as previous and repeat assessments noted at weeks 1, 3, 5 and 9 every 28 days. d: Off-study evaluation. Follow up will be every 6 months for survival.

12.0 Evaluation Criteria/Measurement of Effect

Response Criteria (Primary endpoint is confirmed response rate). To take place >28 days following a response. Otherwise events will be lost).

12.1

12.1.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.1.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
	Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

12.2 Best Response

12.2.1 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).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
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.

13.0 Data Reporting/Protocol Deviations

13.1 Data Reporting

13.1.1 Confidentiality of Records

The original data collection forms will be stored at the originating institution in a secure location. When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act.

13.1.2 Patient Consent Form

At the time of registration, the original signed and dated patient's Informed Consent with the Experimental Subject's Bill of Rights (for the medical record). All Institutional, NCI, Federal, and State of California regulations concerning the Informed Consent form will be fulfilled. }

13.1.3 Data Collection Forms and Submission Schedule

All data will be collected in a timely manner protocol defined case report forms. Data will be sent to the City of Hope Department of Biostatistics and stored in a secure location.

13.1.3.1 Eligibility Checklist

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by a participating investigator prior to registering the patient. See Section 4.3 for the registration procedure.

13.1.3.2 Prior Therapy and On-Study Forms

Within two weeks of registration, the clinical research associate will submit pre-study data collection forms.

13.2 Protocol Deviations

Protocol deviations must be submitted to the Data Coordinating Center. The clinical research associate at COH will also submit copies to the Protocol Management Team and the COH Data and Safety Management Board.

13.2.1 Deviation Policy

In accordance with the COH Policy on Clinical Research Protocol Deviation, there will be a "no deviations" rule for this protocol. However, for subject safety or unforeseen scheduling problems, planned deviations from this protocol will be permitted in accordance with COH IRB policies and if applicable, FDA approval.

13.2.2 Reporting of Unplanned Deviations

All unplanned deviations will be reported to the COH DSMB.

13.2.3 Resolving Disputes

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, the facts of the case will be reported to the DSMB which will be serve as the arbiter of whether a deviation exists.

14.0 Statistical Considerations

14.1 Study Design

The study is an open label, phase II assessment of pazopanib as 3rd-line therapy for mRCC.

14.1.1 Primary Endpoints

The primary endpoint is the confirmed response rate (CR+PR), as determined by the RECIST 1.1 criteria. We will employ the two stage MinMax design suggested by Simon.

Prior data indicates that an overall RR of 20% can be obtained with pazopanib therapy. For patients with mRCC eligible for this 3rd line study, a response rate of 20% would represent a significant improvement over current approaches (3rd line therapy with the Akt inhibitor perifosine, for instance, yielded a 7% response rate) and would further indicate that the activity of pazopanib is maintained through multiple prior lines of therapy in selected patients.

Prior studies suggest that a response rate between 5-10% would not be an improvement over current approaches. As a result, we have set a discouraging response rate at 8%, and an encouraging response rate at 23%. Initially, we will accrue 14 patients. If there is at least 1 responder, accrual will continue to 28 patients. If 5 or more responders (~18%) are observed, pazopanib will be declared promising for future studies, assuming toxicity and survival endpoints are also within acceptable limits. This Simon's MinMax two-stage design has a type I error of 10% (probability of declaring an agent with a true 8% response rate as promising), and a power of 80% (probability of *not* declaring an agent promising with a true 23% response rate is 20%). All eligible patients treated will be included in the calculation of response rate. Any patients with an unknown response rate will be included as a non-responder.

This design has 31% chance of stopping at the first stage if true response rate is 8%.

Toxicity will be monitored on an ongoing basis. If the number of unacceptable toxicities exceeds 1 in the first 3, or exceeds 2 in the first 6 or more than 25% thereafter, the study will hold accrual for an amendment regarding treatment modifications or study termination.

14.1.2 Secondary Endpoints

Secondary endpoints include progression-free survival (PFS), overall survival (OS), and toxicity. Toxicity will use the CTCAE 4.0 and will summarize the worst grade per toxicity, per patient.

Additional secondary endpoints relate to biological correlates, including E-Selection, IL-6, the pre-metastatic niche density, pSTAT3, and baseline HGF. Because the nature of these secondary endpoints is exploratory, we will not consider the issue of multiple comparisons and the according adjustment of p-values.

To determine an association between E-selectin, IL-6 and pre-metastatic niche density, we will conduct a a pairwise correlation test (linear regression). When the sample size is 28, the linear regression test of rho=0 (alpha = 0.050 one-sided) for one normally distributed covariate will have 80% power to detect a correlation coefficient of 0.435.

To determine if the biological correlates (e.g, IL-6, E-selectin, pSTAT3, and HGF), are associated with progression-free survival (PFS), we will fit univariate or multivariate Cox proportional hazards model and report the corresponding p-values. The same method will be employed to evaluate the prognostic effect of pre-metastatic niches.

14.2 Sample Size Accrual Rate

The previously noted sample size of 28 patients is anticipated to accrue over the course of 12 months.

15.0 Human Subject Issues

15.1 Institutional Review Board

In accordance with federal regulations, an Institutional Review Board (IRB) that complies with regulations at 45 CFR 46 and 21 CFR 50, 56 must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

15.2 Recruitment of Subjects

Patients with mRCC will be recruited from patients undergoing evaluation and treatment at City of Hope Cancer Center for this diagnosis.

15.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

15.4 Study location and Performance Sites

This study will be performed at COH.

15.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI).

15.6 Financial Obligations and Compensation

If there is a serious medical complication of the research, treatment will be available at City of Hope, but there will be no compensation to the subject for this injury.

15.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will advise the research subjects about their rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without jeopardizing, include as applicable, their future care or their employment at City of Hope or any relationship they have with City of Hope.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. Following this procedure, the research team will review the results of eligibility testing and determine if the research subject is a candidate for study enrollment.

16.0 References

1. Hurwitz HI, Dowlati A, Saini S, et al: Phase I Trial of Pazopanib in Patients with Advanced Cancer. Clin Cancer Res 15:4220-4227, 2009

2. Motzer RJ, Hutson TE, Tomczak P, et al: Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol 27:3584-3590, 2009

3. Gajiwala KS, Wu JC, Christensen J, et al: KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proceedings of the National Academy of Sciences 106:1542-1547, 2009

4. Nishida T, Takahashi T, Nishitani A, et al: Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene. International Journal of Clinical Oncology 14:143-149, 2009

5. Kay A, Motzer R, Figlin R, et al: Updated data from a phase III randomized trial of everolimus (RAD001) versus PBO in metastatic renal cell carcinoma (mRCC). Presented at the 2009 Genitourinary Cancers Symposium (Abstr 278)

6. Vogelzang NJ, Hutson TE, Samlowski W, et al: Phase II study of perifosine in metastatic renal cell carcinoma (RCC) progressing after prior therapy (Rx) with a VEGF receptor inhibitor. J Clin Oncol 27:15s, 2009 (suppl; abstr 5034)

7. Figlin RA, Hutson TE, Tomczak P, et al: Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). J Clin Oncol 26: 2008 (May 20 suppl; abstr 5024)

8. Escudier B, Pluzanska A, Koralewski P, et al: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 370:2103-11, 2007

9. Escudier BJ, Bellmunt J, Negrier S, et al: Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon-α2a (IFN) in metastatic renal cell carcinoma (mRCC). J Clin Oncol 27:15s, 2009 (suppl; abstr 5020)

10. Rini BI, Halabi S, Rosenberg J, et al: Bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in patients with metastatic renal cell carcinoma: Results of overall survival for CALGB 90206. J Clin Oncol 27:18s, 2009 (suppl; abstr LBA5019)

11. Sternberg CN, Szczylik C, Lee E, et al: A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC). J Clin Oncol (Meeting Abstracts) 27:5021-, 2009

12. Shaw AT, Yeap BY, Mino-Kenudson M, et al: Clinical Features and Outcome of Patients With Non-Small-Cell Lung Cancer Who Harbor EML4-ALK. J Clin Oncol 27:4247-4253, 2009

13. Sandler A, Gray R, Perry MC, et al: Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. N Engl J Med 355:2542-2550, 2006

14. Vickers MM, Choueiri TK, Zama I, et al: Failure of initial VEGF-targeted therapy in metastatic renal cell carcinoma (mRCC): What next? J Clin Oncol 27:15s, 2009 (suppl; abstr 5098)

15. Dham A, Dudek AZ: Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5106

16. Patel JD, Hensing TA, Rademaker A, et al: Phase II Study of Pemetrexed and Carboplatin Plus Bevacizumab With Maintenance Pemetrexed and Bevacizumab As First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol:JCO.2008.20.8181, 2009

17. Spanknebel K, Cheung KY, Stoutenburg J, et al: Initial Clinical Response Predicts Outcome and Is Associated With Dose Schedule in Metastatic Melanoma and Renal Cell Carcinoma Patients Treated With High-Dose Interleukin 2. Annals of Surgical Oncology 12:381-390, 2005

18. Dham A, Dudek AZ: Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5106

19. Hutson TE, Davis ID, Machiels JH, et al: Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor. J Clin Oncol 26: 2008 (May 20 suppl; abstr 5046)

20. Heymach J, Tran HT, Fritsche HA, et al: Lower baseline levels of plasma hepatocyte growth factor (HGF), IL-6 and IL-8 are correlated with tumor shrinkage in renal cell carcinoma patients treated with pazopanib. To be presented at the 2010 American Association of Cancer Research Annual Meeting (Data confidential until presented).

21. Harrison ML, Obermueller E, Maisey NR, et al: Tumor Necrosis Factor {alpha} As a New Target for Renal Cell Carcinoma: Two Sequential Phase II Trials of Infliximab at Standard and High Dose. J Clin Oncol 25:4542-4549, 2007

22. Berntsen A, Trepiakas R, Wenandy L, et al: Therapeutic Dendritic Cell Vaccination of Patients With Metastatic Renal Cell Carcinoma: A Clinical Phase 1/2 trial. Journal of Immunotherapy 31:771-780 10.1097/CJI.0b013e3181833818, 2008

23. Yu H, Jove R: The STATs of cancer [mdash] new molecular targets come of age. Nat Rev Cancer 4:97-105, 2004

24. Xin H, Zhang C, Herrmann A, et al: Sunitinib Inhibition of Stat3 Induces Renal Cell Carcinoma Tumor Cell Apoptosis and Reduces Immunosuppressive Cells. Cancer Res 69:2506-2513, 2009

25. Bedard PL, Body J-J, Piccart-Gebhart MJ: Sowing the Soil for Cure? Results of the ABCSG-12 Trial Open a New Chapter in the Evolving Adjuvant Bisphosphonate Story in Early Breast Cancer. J Clin Oncol 27:4043-4046, 2009

26. Mantovani A, Allavena P, Sica A, et al: Cancer-related inflammation. Nature 454:436-444, 2008

27. Psaila B, Lyden D: The metastatic niche: adapting the foreign soil. Nat Rev Cancer 9:285-293, 2009

28. Erler JT, Bennewith KL, Cox TR, et al: Hypoxia-Induced Lysyl Oxidase Is a Critical Mediator of Bone Marrow Cell Recruitment to Form the Premetastatic Niche. Cancer Cell 15:35-44, 2009

29. Kaplan RN, Riba RD, Zacharoulis S, et al: VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 438:820-827, 2005

17.0 Appendix I: Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

Normal protein excretion is <100 mg to 150 mg/24 hours and is similar for men and women.

Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio ≈ equivalent to grams of protein excreted in urine over 24 hrs.

Example: Patient has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio= (90 mg/dL) / (30 mg/dL) = 3

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

Units for UPC ratio

Note: To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or µmol/L). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in µmol/L, conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: µmol/L	Multiply by 88.4
SI Units: µmol/L	Conventional Units: mg/dL	Divide 88.4

References:

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

NKF: NKF KDOQI Guidelines [Internet]. National Kidney Foundation; nd. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Available from http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm

Appendix II: Determination of Creatinine Clearance (Cl_{CR})

Estimation of creatinine clearance using Cockroft and Gault method:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

Cl_{CR} for females (mL/min) = $\frac{(0.85) \times [140 - \text{age (years)}] \times [\text{weight (kg)}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$

For SI units:

Cl_{CR} for males (mL/min) = $\frac{[140 - \text{age (years)}] \times [\text{weight(kg)}] \times (1.23)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

Cl_{CR} for females (mL/min) = $\frac{[140 - \text{age(years)}] \times [\text{weight(kg)}] \times (1.05)}{[\text{serum creatinine } (\mu\text{mol/L})]}$

Calculation of creatinine clearance based on 24-hour urinary creatinine excretion and concurrent serum creatinine levels:

$$Cl_{CR} = \frac{C_U \cdot V}{C_{CR}}$$

Here, C_U is the concentration of creatinine in the urine (mg/dL or µmol/L, for SI units), V is the urine volume (in mL per minute of urine produced during the collection period), C_{CR} is the serum creatinine concentration (mg/dL or µmol/L, for SI units), and Cl_{CR} is the creatinine clearance in mL per minute.

Appendix III: New York Heart Association (NYHA) Classifications

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 2228.

Appendix V: ECOG Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

18.0 Patient Monitoring and Management Guidelines for Certain Treatment Emergent Adverse Events of Interest (AEOIs)

18.1 Diarrhea

In cancer patients, diarrhea can be debilitating and potentially life threatening, with dehydration, renal insufficiency, and electrolyte imbalances. Pazopanib as a monotherapy has been associated with an increased incidence of diarrhea, which is grade 1 or 2 in the majority with grade 3/4 diarrhea occurring in approximately 4% of subjects. The incidence and severity may increase when administered with other agents known to cause diarrhea.

Early identification and intervention is critical for the optimal management of diarrhea. Please refer to Supportive Care Guidelines for Diarrhea in Appendix I, Section 19.1 for detailed management guidelines. A subject's baseline bowel pattern should be established so that changes in that pattern can be identified. In addition, subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

Appendix 1: Supportive Care Guidelines

Diarrhea

The NCI CTCAE Version 4.0 criteria for defining diarrhea are provided below.

Toxicity Grade	**Diarrhea (includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea)**
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; IV fluids indicated < 24 h; moderate increase in ostomy output compared to baseline; not interfering with daily living
3	Increase of ≥7 stools/day over baseline; incontinence; IV fluids ≥ 24 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living
4	Life threatening consequences (e.g., hemodynamic collapse)
5	Death

Uncomplicated diarrhea is considered mild to moderate and defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with 1 or more of the following signs or symptoms; cramping, nausea/vomiting, ≥ Grade2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, and/or dehydration. If complicated diarrhea goes unrecognized or untreated, it may lead to death.

Experience thus far suggests that, when pazopanib is used as monotherapy, uncomplicated CTCAE Grade 1 or 2 diarrhea may ensue. In rare cases, subjects treated with monotherapy pazopanib may develop

debilitating and potentially life-threatening diarrhea with dehydration, renal insufficiency, and electrolyte imbalances. The pathophysiologic mechanism of diarrhea with pazopanib is not known.

The following broad general management principles are recommended as means by which a subject with diarrhea may avoid more serious complications. Guidelines such as these should never replace sound clinical judgment. Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea [Benson, 2004]. The guidance provided here is a modification of the ASCO guidelines..

Early identification and intervention is critical for the optimal management of diarrhea.

- A subject's baseline bowel pattern should be established so that changes in that pattern can be identified.

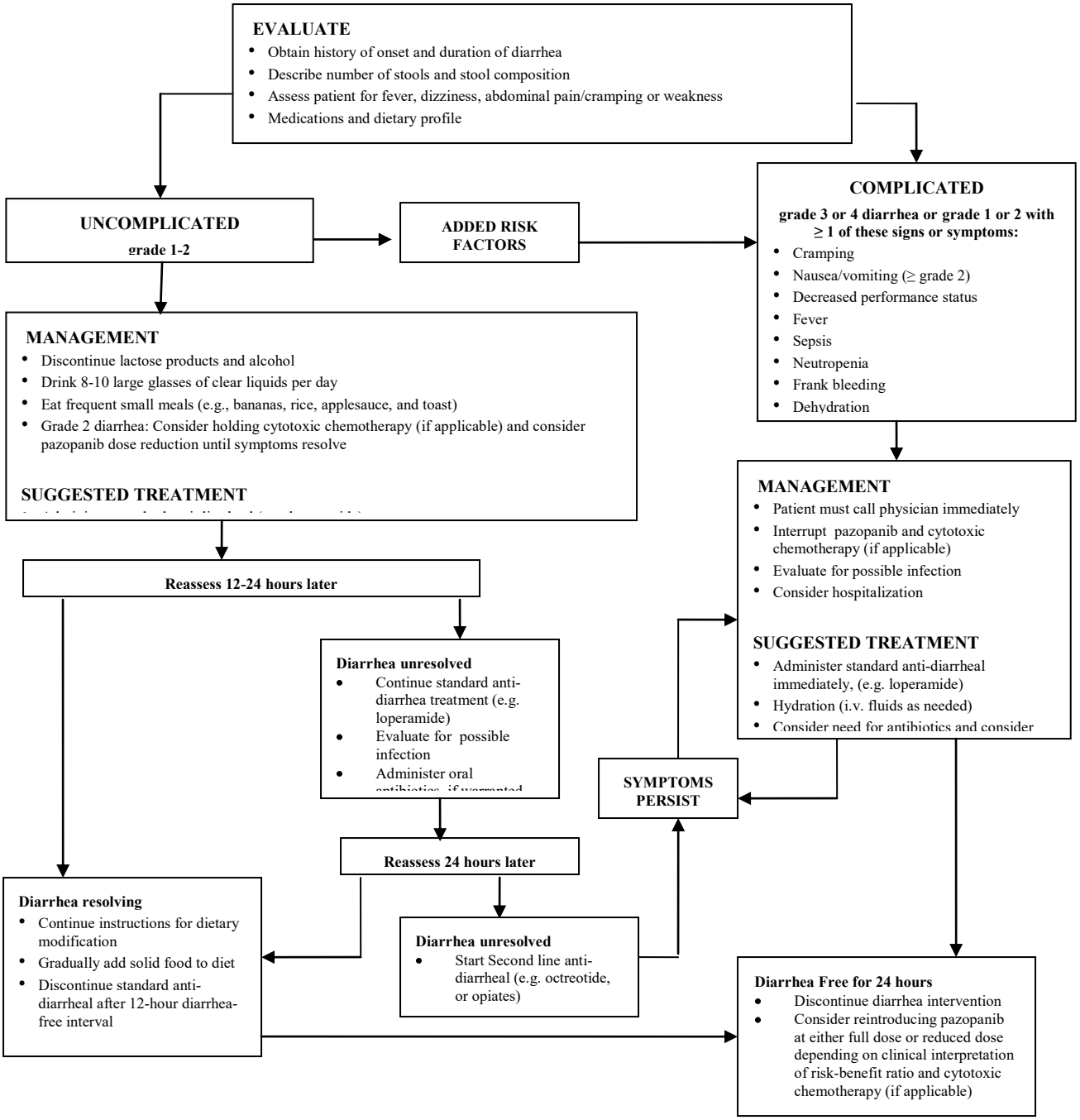
- Subjects should be educated on the signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

- At the initiation of diarrhea, an assessment of frequency, consistency, duration and other symptoms such as fever, cramping pain, nausea, vomiting, dizziness and thirst should be taken to identify subjects at high risk of complications.

Several treatments have demonstrated efficacy in diarrhea management:

- Loperamide, administered as an initial 4-mg dose, followed by 2-mg doses after every unformed stool with a maximum of 16mg per day. This dose and regimen are moderately effective. Continuation of loperamide is suggested until the subject is diarrhea-free for 12 hours. Dose should not exceed a maximum of 8 tablets (16 mg) per day.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. In the treatment of chemotherapy-induced diarrhea, octreotide can be administered at doses ranging from 100μg twice daily to 500μg 3 times daily, with a maximum-tolerated dose of 2000μg 3 times daily in a 5-day regimen. However, the effect of octreotide on diarrhea associated with use of pazopanib is unknown.

Figure 1. Generic flow chart for suggested management of Diarrhea


EVALUATE
Obtain history of onset and duration of diarrhea
Describe number of stools and stool composition
Assess patient for fever, dizziness, abdominal pain/cramping or weakness
Medications and dietary profile
UNCOMPLICATED
grade 1-2
ADDED RISK FACTORS
COMPLICATED
grade 3 or 4 diarrhea or grade 1 or 2 with ≥ 1 of these signs or symptoms:
Cramping
Nausea/vomiting (≥ grade 2)
Decreased performance status
Fever
Sepsis
Neutropenia
Frank bleeding
Dehydration
MANAGEMENT
Discontinue lactose products and alcohol
Drink 8-10 large glasses of clear liquids per day
Eat frequent small meals (e.g., bananas, rice, applesauce, and toast)
Grade 2 diarrhea: Consider holding cytotoxic chemotherapy (if applicable) and consider pazopanib dose reduction until symptoms resolve
SUGGESTED TREATMENT
MANAGEMENT
Patient must call physician immediately
Interrupt pazopanib and cytotoxic chemotherapy (if applicable)
Evaluate for possible infection
Consider hospitalization
SUGGESTED TREATMENT
Administer standard anti-diarrheal immediately, (e.g. loperamide)
Hydration (i.v. fluids as needed)
Reassess 12-24 hours later
Diarrhea unresolved
Continue standard anti-diarrhea treatment (e.g. loperamide)
Evaluate for possible infection
Administer oral
SYMPTOMS PERSIST
Reassess 24 hours later
Diarrhea resolving
Continue instructions for dietary modification
Gradually add solid food to diet
Discontinue standard anti-diarrheal after 12-hour diarrhea-free interval
Diarrhea unresolved
Start Second line anti-diarrheal (e.g. octreotide, or opiates)
Diarrhea Free for 24 hours
Discontinue diarrhea intervention
Consider reintroducing pazopanib at either full dose or reduced dose depending on clinical interpretation of risk-benefit ratio and cytotoxic chemotherapy (if applicable)

Nausea and Vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib.

Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.

If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next scheduled dose on the following day. . If vomiting persists then the subject should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. Depending upon approved medications in your region, these may include: 5-HT_3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones, prednisone); and cannibinoids (dronabinol).

References:

Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Inducted Diarrhea. J Clin Oncol. 2004, 22; 2918-26.