

Title: An expanded Phase I study of pazopanib and everolimus in patients with advanced solid tumors and previously treated advanced urothelial cancer.

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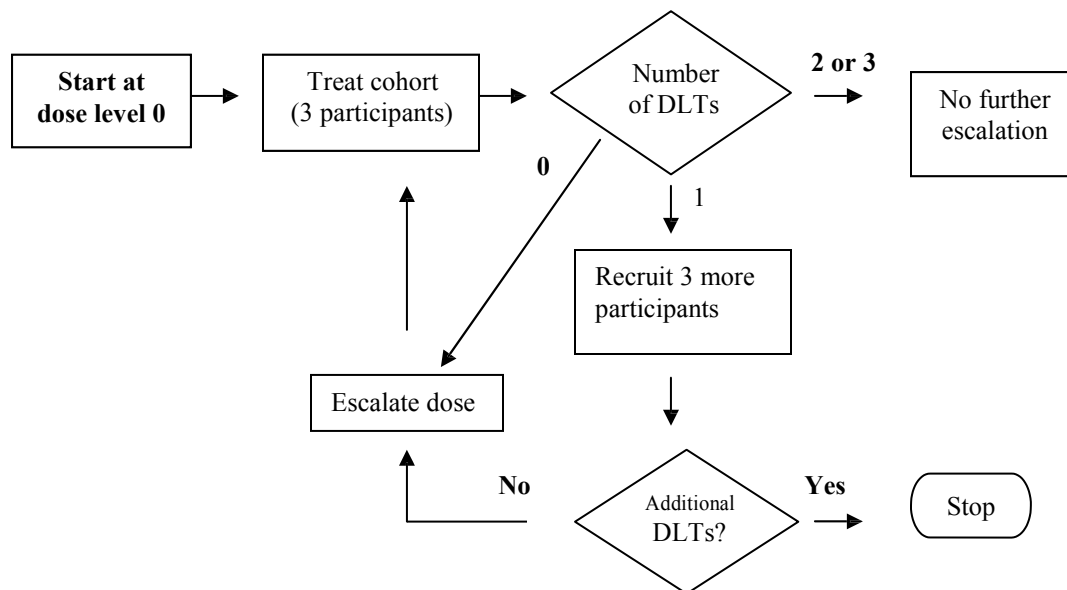
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Everolimus (NSC 733504; IND 79, 707) – Novartis

SCHEMA

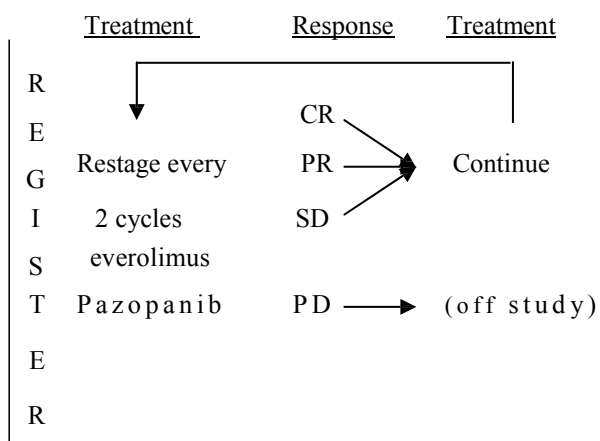
Phase I Portion



Expansion Cohort

Definitions

CR - Complete Response
PR - Partial Response
PD - Progressive Disease
SD - Stable Disease



1 cycle = 28 days

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1. OBJECTIVES

1.1 Study Design

This is a Phase I study with an expansion cohort in advanced urothelial cancer patients. The Phase I portion of the study was an open-label standard 3+3 dose escalation study to determine the maximum tolerated dose (MTD) of the combination of pazopanib (GW786034) and everolimus in patients with solid tumors who have no standard treatment options available. Starting doses will be set at everolimus 5 mg PO QD and pazopanib 400 mg PO QD. Cycle length will be 4 weeks. One dose de-escalation will be allowed if the MTD is exceeded in dose level 0 (indicated as dose level -1). Initial phase I testing identified pazopanib 400 mg PO daily and everolimus 5 mg PO daily as the MTD. Based on the phase I response data, an expansion cohort of 25 patients with metastatic urothelial cancer who have received prior chemotherapy, but no prior mTOR or VEGF inhibitors, will be enrolled.

The protocol is being amended to accrue urothelial carcinoma patients rather than kidney cancer patients in the expansion cohort given the significant unmet need in urothelial carcinoma and findings of significant activity of the regimen in at least a subset of urothelial carcinoma patients,

The primary endpoint of the expansion cohort will be objective response proportion with secondary endpoints including safety, progression-free survival, and duration of response.

1.2 Phase I study

1.2.1 Primary Objective

To determine the maximum tolerated dose and dose limiting toxicities of the combination of pazopanib and everolimus.

1.2.2 Secondary Objective

To determine the pharmacokinetics of the combination of pazopanib and everolimus.

1.3 Expansion Cohort (Urothelial Carcinoma)

1.3.1 Primary objective

To determine the objective response rate in patients with locally advanced or metastatic urothelial cancer who have had previous treatment with cytotoxic chemotherapy.

1.3.2 Secondary Objectives

1.3.2.1 To determine the safety, progression-free survival, and duration of response of pazopanib and everolimus in patients with metastatic urothelial cancer.

1.3.3 Exploratory Objective

1.3.2.2 To perform either whole exome or targeted sequencing of selected genes to evaluate whether somatic DNA alterations are associated with response or progression with pazopanib and everolimus treatment.

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Everolimus

Everolimus, a novel oral derivative of rapamycin, has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. Everolimus has been in development for patients with various malignancies since 2002. Everolimus was FDA approved in 2009 (Afinitor®) for the treatment of kidney cancer that has progressed after sunitinib or sorafenib. Everolimus is being investigated as an anticancer agent based on its potential to act:

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

At weekly and daily schedules and at various doses explored, RAD0001 is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

2.1.1.1 mTOR pathway and mechanism of action

At cellular and molecular level everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), a key and a highly conserved serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of everolimus (Reviewed in Boulay and Lane, 2007)¹. mTOR is downstream of PI3K/AKT pathway, a pathway

known to be dysregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness, resistance to treatment and progression. The main known functions of mTOR include the following^{1,2}:

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.
- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates translation of important messages, including those encoding the HIF-1 proteins, c-myc, ornithine decarboxylase, and cyclin D1, as well as ribosomal proteins themselves.
- The activation of mTOR pathway leads to the increased production of pro-angiogenic factors (i.e., VEGF) in tumors and to tumor, endothelial and smooth muscle cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

mTOR is represented by two structurally and functionally distinct multi-protein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive).³ mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2).² Activated AKT phosphorylates TSC2, which lead to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1.⁴ mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signaling.⁴ It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT, which is not upstream of mTORC1. PHLPP phosphatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton.³

mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as everolimus. Once these agents bind to the 12 kDa cytosolic FK506-binding protein immunophilin FKBP12, the resulting rapamycin-FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling

events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity. As many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis.²

2.1.1.2 Preclinical studies

Pre-clinical investigations have demonstrated that everolimus is a potent inhibitor of the proliferation of a range of human tumor cell lines *in-vitro* with IC50s ranging from sub/low nanomolar to micromolar concentrations, concentrations capable of being reached in patients at the doses used in clinical trials.

Everolimus was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma), Everolimus inhibited colony formation in a concentration-dependent manner. In addition, normal hematopoietic stem cells were insensitive to everolimus, with an IC50 about 15 fold higher than the tumor lines. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF-induced proliferation. The inhibition of endothelial proliferation and antiangiogenic activity of everolimus was confirmed *in vivo*, as everolimus selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls at well tolerated doses. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus- treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

Everolimus also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of everolimus monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease. Everolimus, administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- subcutaneous mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170 over-expressing multi-drug resistant tumor line;
- in a series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3

- lines), lung (22 lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines);
- in two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma)

Taken together, these data indicate the broad anti-proliferative potential of everolimus.

It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein. PTEN status alone may not be predictive of everolimus relative *in vitro* sensitivity, however in some cases (i.e., GBM) there is also a correlation with PTEN status. In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

2.1.1.3 Pre-clinical safety

In safety pharmacology studies, everolimus was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. Everolimus had no influence on QT interval prolongation. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of everolimus to affect vital functions in patients is considered to be low. Everolimus is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with everolimus in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

2.1.1.4 Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. The coefficient of variation between patients is approximately 50%. Trough levels (24 hour post-dose) correlate well with $AUC_{0-\tau}$ at steady-state during daily administration.

In whole blood, at a daily dose of 10 mg, about 20% of everolimus is confined in plasma with 26% being unbound. The remaining 80% is sequestered in blood cells.

Everolimus is extensively metabolized in the liver and eliminated in the bile. Major metabolites are inactive. Elimination half-life is approximately 30 hours. The clearance of everolimus is approximately halved in patients with mild-moderate hepatic impairment (Child-Pugh Class A or B), while renal impairment has little or no impact on the pharmacokinetics of everolimus. Age, weight and gender in the adult population do not affect the pharmacokinetics of everolimus to a clinically relevant extent. The clearance of everolimus is reduced in children. Pharmacokinetic characteristics are not notably different between Caucasian and Japanese subjects, whereas in Black patients population pharmacokinetic studies have shown an average 20% higher clearance. A high-fat meal altered the absorption of everolimus with 1.3 hour delay in t_{max} , a 60% reduction in C_{max} and a 16% reduction in AUC.

Everolimus is a substrate of CYP3A4 and a substrate and a moderate inhibitor of the multi-drug efflux pump P-glycoprotein (P-gP, MDR1, ABCB1). Hence, its metabolism is sensitive to drugs which modify these enzymes (substrates, inducers, or inhibitors of these enzymes). Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 or P-glycoprotein substrates. Section 5.4.5 lists examples of clinically relevant CYP3A inhibitors and inducers. Please refer to Section 5.4.5 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications. More information on everolimus pharmacokinetics is provided in the Investigator's Brochure.

2.1.1.5 Everolimus Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition. Furthermore, molecular pharmacodynamic (MPD) studies, using immunocytochemistry (IHC) in biopsied tumor tissue, assessed the degree of inhibition and its duration for pS6, p4E-BP1 and pAKT expression with the daily and weekly dosing. There was high inhibition of the downstream markers S6K1 and 4E-BP1 at 5mg/day, which was complete at 10 mg/day, while preliminary results suggest increase in pAKT expression with maximal effect at 10 mg daily⁵. More information is provided in the Investigator's Brochure.

2.1.1.6 Clinical experience with everolimus

Everolimus has been investigated as a component of multi-drug immunosuppression in solid organ transplantation since 1996 and was approved for the indication of prophylaxis of organ rejection in adult patients receiving an allogeneic renal or cardiac transplant on 8 Jul 2003 by the European Union under the trade name of Certican®. The most frequent adverse drug reactions in this context are highly specific to the transplant context.

However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels.

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Afinitor® was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor® was approved for “progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease” in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Approximately 25,645 cancer patients have been treated with everolimus as of 30-Sep-2012:

- 13,229 patients in Novartis-sponsored clinical trials
- 2,624 patients in the individual patient supply program
- 9,792 patients in investigator-sponsored studies.
- In addition, healthy volunteer subjects and non-oncology hepatically impaired subjects have participated in the clinical pharmacology studies as described in Section 7.2.

A phase II study of single agent everolimus in locally advanced or metastatic urothelial cancer after failure of platinum based chemotherapy reported a response rate of 5% in this setting (Partial response in 2 of 37 patients). (6)

Overall, the most frequent mild-moderate Grade 1/2 adverse effects have been rash, stomatitis, fatigue, neutropenia and to a lesser extent gastrointestinal disorders (nausea, anorexia, diarrhea, vomiting), and headache. The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia. Reduced blood counts, hyperlipidemia (mainly hypercholesterolemia) and hyperglycemia are relatively frequent laboratory findings. Infections have not been notably frequent or severe. Non-infectious low- Grade (Grade 1/2) pneumonitis has led to development of treatment guidelines for the disorder (Section 6.2.3). Further detailed information regarding

everolimus clinical development, safety and efficacy is provided in the Investigator's Brochure.

2.1.2 Pazopanib (GW786034)

Pazopanib is a potent, multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR-1, -2, -3, PDGFR- α and - β and c-kit, with half-maximal inhibition (IC_{50}) values of 10, 30, 47, 71, 84 and 74nM, respectively. It inhibits VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells (HUVEC) as well as in mouse lungs in a dose-dependent manner. Data from preclinical studies show pazopanib has significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibits basic fibroblast growth factor-(bFGF-) and VEGF-induced angiogenesis in two mouse models of angiogenesis, viz., the Matrigel plug assay and the cornea micropocket model.

2.1.2.1. Safety

As of September 2007, approximately 1400 cancer subjects have received pazopanib in clinical studies. The most common adverse events (AEs) reported to date include diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (NCI-CTCAE). The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon.

The most common serious adverse events (SAEs) occurring in subjects enrolled in pazopanib studies regardless of treatment assignment include vomiting, diarrhea, abdominal pain, hypertension/hypertensive crisis, dyspnea, pleural effusion, pyrexia, anemia, dehydration, and pulmonary embolism. Evaluation of the safety and efficacy of pazopanib in advanced RCC subjects include a recently completed Phase II study in subjects with advanced RCC, and a Phase III randomized, double-blind study against placebo which completed enrolment in April, 2007 and is currently on-going. To date, 660 subjects with advanced/metastatic RCC have been enrolled in these two clinical trials. Safety data from the Phase II RCC trial VEG102616 (n=225) are summarized here. The most common AEs (defined as AEs experienced by $\geq 10\%$ of subjects) regardless of causality in decreasing order of frequency were diarrhea (63%), fatigue (46%), hair color change (43%), nausea (42%), hypertension (41%), anorexia (24%), dysgeusia (24%), vomiting (20%), headache (20%), cough (17%), abdominal pain, (16%), rash (16%), constipation (15%) ALT elevation (14%), arthralgia (13%), AST elevation (12%), back pain (12%), dizziness (12%), handfoot syndrome (11%), alopecia, (10%), dyspepsia (10%), and peripheral edema (10%). The majority of these events were Grade 1 and 2 with hypertension being observed in 9% of subjects as a Grade 3 event.

The most common hematological toxicities of any grade (graded according to NCICTCAE) include lymphopenia (47%), thrombocytopenia (28%), neutropenia (23%), and anemia (26%) with combined Grade 3 and 4 abnormalities occurring in 7%, 3%, <1%, and 4% of subjects, respectively. The most common chemistry abnormality was hyperglycemia, observed in 46% of subjects (of which 2% were Grade 3 and no Grade 4). Hyponatremia of any grade was observed in 37% of subjects, with Grade 3 or Grade 4 hyponatremia in 8% of subjects. Hyperkalemia of any grade was reported in 27% of subjects, with Grade 3 or 4 hyperkalemia in 5% of subjects. Hyponatremia and hyperkalemia have not occurred concurrently in the same subject to indicate adrenal insufficiency. Elevations in amylase and lipase of any grade were reported in 23% and 27% of subjects, respectively, with Grade 3 or Grade 4 events in 4% and 9% of subjects, respectively. There were 2 reports of pancreatitis. Increase in TSH was reported in 28% of subjects and a decrease in thyroxine (T4) in 1% of subjects. Three subjects initiated treatment with thyroid replacement therapy (synthroid or levothyroxine) during the study. ALT elevations of any Grade were reported in 53% of subjects with Grade 3 and Grade 4 elevations in 9% and <1% of subjects, respectively. AST elevations were reported in 53% of subjects with Grade 3 and Grade 4 elevations in 5% and <1% of subjects, respectively. Hyperbilirubinemia of any Grade occurred in 28% of subjects with Grade 3 elevations in <1% of subjects. No Grade 4 elevations have been reported. Concomitant elevations in transaminases and bilirubin have been observed in 2 (<1%) subjects. Neither of these patients met the criteria for Hy's rule. Risk factors that may have contributed to the liver dysfunction were identified in the some of these subjects, (e.g., large mass at the porta hepatis, hepatotoxic concomitant medications). Liver enzyme elevations were reversible upon dose interruption. Two patterns of transaminase changes have been observed: (1) transaminase elevations that declined over time without dose interruption. (2) transaminase elevations that declined over time upon dose interruption. In some subjects, elevations in transaminase recurred upon rechallenging and these subjects were permanently discontinued from study treatment. Serial adrenocorticotrophic hormone (ACTH) stimulation tests were conducted in two Phase I and two Phase II trials in cancer subjects with data available in 47 subjects. Twenty-one of them had data beyond 24 weeks and 5 subjects had data beyond 52 weeks. None of these 47 subjects had adrenal insufficiency.

Certain uncommon AEs with significant clinical consequences reported in pazopanib clinical trials (denominator for total subject enrolment n=1000 used for calculating frequency) include pulmonary embolism (0.6%), venous thrombosis (0.3%), venous thrombosis and pulmonary embolism (0.2%), serious hemorrhage (1.4%), bowel perforation (0.5%), myocardial infarction/angina (0.7%), cerebrovascular accidents/transient ischemia (0.6%), cardiac failure (0.2%), atrial fibrillation (0.3%), renal failure (0.8%) and seizures (0.3%).

2.1.2.2. Preliminary Efficacy Summary

VEG102616 is a Phase II study to evaluate the efficacy and safety of pazopanib in subjects with advanced/metastatic RCC. Of the 225 subjects enrolled, 155 (69%) had no prior systemic therapy, and 70 (31%) had 1 prior therapy of either a cytokine or bevacizumab

based therapy. The study utilized a randomized discontinuation design that includes a 12-week lead-in phase during which all subjects received 800mg pazopanib daily dose. Based on the disease assessment at Week 12, subjects with a complete or partial response would continue pazopanib treatment until disease progression; subjects with progressive disease (PD) at or prior to Week 12 would discontinue pazopanib treatment; and subjects with stable disease (SD) at Week 12 were randomized to receive blinded treatment with 800mg pazopanib or placebo for 16 weeks. An interim analysis was performed in September 2006 when the first 60 enrolled subjects had completed the 12-week Lead-In phase. Based on the review of both interim efficacy (12-week response rate) and safety data from this study, the Independent Data Monitoring Committee recommended halting further randomization, unblinding the study and offering pazopanib treatment to subjects on the placebo arm of the randomization phase of the study. As a result randomization at 12 wks was discontinued, subjects previously randomized to placebo were crossed over to pazopanib, and all subjects could receive pazopanib until progressive disease (PD), unacceptable toxicity, or consent withdrawal.

In 2009, the FDA granted approval to pazopanib for the treatment of patients with advanced renal cell carcinoma. This was based on the results of a phase III international, randomized, double-blind trial comparing pazopanib to placebo in patients with previously untreated advanced renal cell carcinoma or patients who had progressed on cytokine therapy. This study demonstrated a progression-free survival advantage of 9.2 months with pazopanib vs. 4.2 months with placebo(7). In 2012 the PISCES phase III randomized trial results were presented at the annual European society of Medical Oncology meeting, In this study the tolerability of pazopanib was compared to sunitinib and results showed that pazopanib was associated with significantly better health related quality of life compared to sunitinib and it resulted in less fatigue and less dysgeusia. In 2012, the FDA approved pazopanib hydrochloride tablets for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy after it was shown to improve median PFS to 4.6 months for patients receiving pazopanib hydrochloride compared with 1.6 months for patients receiving placebo in a phase III study.

2.2 Study Disease

While front-line cisplatin-based combination chemotherapy is highly active, more than 85% of patients will relapse following initial therapy. There is no standard 2nd-line regimen following failure of front-line chemotherapy. Many agents, including docetaxel, paclitaxel, pemetrexed, and ifosfamide, have shown single agent responses (between 10-20%, which improve with combination therapy), yet no randomized trial has shown the benefit of one over another. In fact, no second-line trial has demonstrated improved survival with any chemotherapy agent.

The importance of angiogenesis in invasive and advanced urothelial cancer is well documented. Increased microvessel density has been shown to predict advanced disease and poor prognosis in urothelial cancer.¹⁰⁻¹⁷ Preclinical models in bladder cancer suggest that anti-angiogenic therapies

may inhibit progression of bladder cancer.¹⁸ VEGF appears to be a major angiogenic factor in urothelial carcinoma.^{15,19-21} The importance of angiogenesis in invasive TCC is well documented. Both VEGF mRNA and protein are over-expressed in advanced bladder cancer compared with normal bladder epithelium.²²⁻²⁴ In addition to its pro-angiogenic properties, recent in vitro experiments also suggest a role for VEGF signaling as an autocrine and paracrine growth factor to directly promote bladder cancer growth.²⁵ Furthermore, retrospective evaluation of serum VEGF levels in the metastatic setting appears to correlate high levels with poor disease-free survival.²⁶ Baseline VEGF mRNA expression levels and microvessel density were found to be independent prognostic factors for recurrence and metastasis in 51 patients treated with neoadjuvant MVAC chemotherapy and cystectomy.¹¹ In addition to its pro-angiogenic role, elevated levels of VEGF in tumors lead to abnormal microvasculature. Excessive angiogenic factors recruit endothelial and perivascular cells to form tortuous and dilated blood vessels with poor rheological characteristics, leading to abnormal tumor blood flow. Elevated VEGF levels in tumors leads to increased vascular permeability.²⁷ By reducing VEGF levels, not only are the aberrant tumor-associated blood vessels eliminated, but the microvasculature also appears to be remodeled, leading to more “normal” blood vessel architecture. This leads to improved transvascular drug delivery directly to tumor cells.

VEGF inhibition alone, which primarily targets endothelial cells does not appear to be sufficient as an anti-cancer strategy in advanced urothelial carcinoma. Sunitinib and pazopanib have shown modest activity as single agents, with few patients having objective responses, and rates of stable disease are low.²⁸⁻³¹ Nearly all patients progress on these agents, and the majority of patients do not have any significant disease response or stabilization.

Autocrine and paracrine growth signals to cancer cells are frequently mediated via the PI3 kinase/Akt pathway.³² PI3 kinase activity results in membrane localization of Akt, leading to the generation of activated phospho-Akt. This activated Akt phosphorylates and inactivates TSC2. TSC1 and TSC2 form a complex that normally suppresses signaling through mTOR. Inactivation of TSC2 results in increased signaling through the mTOR complex, which then leads to increased cell metabolism, growth, and survival. These effects appear to be abrogated by mTOR inhibition with rapamycin.³³ In addition, mTOR may also be directly activated by Akt.³⁴

The PI3 kinase/Akt/mTOR pathway is frequently activated in advanced urothelial carcinoma specimens.^{35,36} mTOR pathway signaling appears active in many urothelial carcinoma specimens³⁷ and appears associated with worse survival.³⁸ In addition, deletion of chromosome 9q spanning the region containing TSC1 is the most frequent genetic alteration in transitional cell carcinoma.³⁹ TSC1 is believed to represent a tumor suppressor gene deleted at that site. Inactivating mutations are observed in TSC1 in 10-30% of cases.^{40,41}

In addition to chromosome 9q and TSC1 alterations, chromosome 10q loss is frequent in transitional cell carcinoma. PTEN, a negative regulator of the Akt pathway located on chromosome 10q, shows loss of heterozygosity in approximately 25% of transitional cell carcinomas, as well as homozygous deletions and point mutations in a small subset of cases.^{42,43} Bladder cancer has also been reported in patients with Cowden disease, caused by autosomal dominant mutations in PTEN.^{44,45}

Preclinical evaluation of mTOR inhibition with everolimus demonstrates that it inhibits urothelial carcinoma cells in vitro⁴⁶, although did not affect the growth of urothelial carcinoma in a chemically-induced mouse urothelial carcinoma model⁴⁷. A phase II trial of everolimus as a single agent enrolled 45 patients. Two partial responses were noted.⁴⁸, suggesting modest activity of this agent.

Based on these data, the PTEN/PI3 kinase/Akt/mTOR pathway may play an important role in transitional cell carcinoma, and inhibition of this pathway may be therapeutically useful in advanced transitional cell carcinoma patients. The utility of these agents in combination with anti-VEGF agents has not yet been thoroughly tested, as synergy between these pathways is predicted.

2.3 Rationale

Dose Escalation Cohort: Both anti-angiogenic therapy and mTOR inhibition provide significant clinical benefit in metastatic kidney cancer patients, although responses to each therapy are limited in duration and extent.

Expansion Cohort: There are no standard therapies available for patients with metastatic urothelial carcinoma who have progressed following front-line chemotherapy. Novel approaches are needed.

Currently approved anti-VEGF tyrosine kinase inhibitors exhibit significant side effects, including rash, diarrhea, endocrine abnormalities, cardiotoxicity, and fatigue. Pazopanib appears to have a somewhat improved therapeutic index and may be associated with less toxicity yet with comparable efficacy.

Pazopanib has been tested in a randomized discontinuation study in patients with metastatic clear cell renal cell carcinoma. Pazopanib has resulted in 40% of patients with a partial response to induction therapy, and a significant improvement in progression free survival in patients randomized to active drug in the randomized discontinuation portion of the protocol.

The most prominent significant toxicity observed has been hypertension. Hepatotoxicity may be higher with this agent but fewer dermatologic and gastrointestinal toxicities have been observed compared to other anti-VEGF tyrosine kinase inhibitors. The lower toxicity, enhanced tolerability, and high activity of pazopanib make it an ideal candidate to combine with other targeted therapies.

Addition of another agent targeting other anti-angiogenic pathways may provide either additive or synergistic effects with existing anti-VEGF agents. Downstream signal transduction inhibition of the PTEN/Akt/mTOR pathway by everolimus may complement upstream VEGF receptor

inhibition by either simple additive effects when both targets are inhibited, or by downstream blockade of pathways if there is partial resistance to receptor inhibition. Loss of PTEN function via methylation is common in metastatic kidney cancer and appears common in bladder cancer, leading to increased Akt activity and cell proliferation.⁴⁹ Activation of mTOR, a downstream effector of Akt, has been shown in preclinical models to increase tumor cell proliferation and promote angiogenesis. Everolimus, an oral inhibitor of mTOR, decreases tumor and endothelial cell proliferation and tumor cell VEGF production, leading to antitumor and potential anti-angiogenic effects. In phase I studies, objective tumor responses with everolimus have been seen in a variety of tumor types. Combination of everolimus with angiogenesis inhibitors in preclinical studies has led to synergistic anti-angiogenic and antitumor effects.⁵⁰ Although pre-clinical studies with everolimus and pazopanib in combination have not been done, the pre-clinical evidence of synergy between anti-VEGF and anti-mTOR drugs provides the rationale to test everolimus in combination with pazopanib. Everolimus is FDA approved for the treatment of advanced kidney cancer, pancreatic neuroendocrine tumors, and subependymal giant cell astrocytomas. – In 2012 Afinitor® (received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Everolimus is a substrate of CYP3A pathways, and a competitive inhibitor of CYP3A and CYP2D6 enzymes. These potential interactions require pharmacokinetic evaluation of drug levels of both everolimus and pazopanib. As a result, pharmacokinetic data for both drugs will be obtained at day 1 and 15 of cycle 1 for all patients on the phase I portion of this study.

The starting dose for the initial Phase 1 cohort was chosen as 3/4 of the standard single-agent dose of pazopanib, and half-dose of everolimus, primarily based on available pill size. While these starting doses were arbitrary, they were both at levels consistent with activity against the targets as single agents.

For the dose escalation cohort: Escalation occurred in a 200 mg increment for pazopanib up to the standard dose of 800 mg daily. Everolimus will be escalated from 5 mg to 10 mg. One drug is escalated alternately in each successive cohort. De-escalation will be allowed to dose level -1 if there are excessive DLT's observed in the starting dose level. In addition, dose level +2A will be considered if there is a DLT at dose level +2. This dose level would test full dose pazopanib 800 mg daily in combination with everolimus 5 mg daily.

Phase I update as of 3/19/14

The first portion of this study of everolimus plus pazopanib in genitourinary and other solid malignancies was carried out at the Dana-Farber Cancer Institute. Nine patients were enrolled of which five had urothelial carcinoma of the bladder. These nine patients were either treated on Dose Level 0: Pazopanib 600 mg PO QD and everolimus 5 mg PO QD (n=3) or Dose Level -1: Pazopanib 400 mg PO QD and everolimus 5 mg PO QD (n=6). Pharmacokinetic data were collected on everolimus and pazopanib to determine whether drug-drug interactions occur. These data are from the 5 patients (3 lung cancer, 2 bladder cancer, 1 adrenal cortical carcinoma) treated with pazopanib 400 mg daily and everolimus 5 mg daily (Dose Level -1). The Day 15 steady-state whole blood everolimus PK parameters were:

| | everolimus (mean ± SD values) | O'Donnell, et al JCO 2008(51) (mean ± SD values) |
|---------------------------|--|---|
| AUC _{ss} (0-24h) | 335 ± 189 ng*h/mL (median, 348 ng*h/mL; range, 162-868 ng*h/mL). | 238 ± 77 ng*h/mL |
| C _{max,ss} | 37.9 ± 2.1 ng/mL | 32 ± 9 ng*h/mL |
| C _{min,ss} | 6.1 ± 4.9 ng/mL | 5.4 ± 1.8 ng/mL |

The percent difference between the mean values of the steady-state PK parameters for everolimus given in combination with pazopanib relative to everolimus alone were: +13% for C_{min,ss}, +18% for C_{max,ss}, and +100% for AUC_{ss}(0-24h). These findings demonstrate a significant pharmacokinetic interaction between the two drugs resulting in a marked decrease in the apparent clearance of everolimus. Pharmacokinetic data for pazopanib from the phase I combination trial indicates that there is no effect of everolimus on pazopanib pharmacokinetics when evaluated in the context of known pazopanib pharmacokinetic data:

| | Pazopanib (CV, %) | Hurwitz, et al. Clin Canc Res 2009 (CV, %) |
|----------------------------------|------------------------------|---|
| AUC ₀₋₂₄ (µg·h/mL) | 451.6 (41.2) | 447.1 (31.3) |
| C _{max} (µg/mL) | 26.8 (35.5) | 21.8 (56.3) |
| C ₂₄ (µg/mL) | 13.9 (49.8) | 10.4 (86.6) |

Toxicity

Nine patients were enrolled in the phase I portion of this study. Two patients on dose level 0 (pazopanib 600 mg daily and everolimus 5 mg daily) experienced dose limiting toxicities (grade 3 rash and pruritus and grade 3 thrombocytopenia requiring a dose reduction). Therefore, three patients were treated at dose level -1 per protocol. None of these three patients experienced a protocol-defined dose-limiting toxicity. Therefore, another three patients were treated at dose level -1 (pazopanib 400 mg daily and everolimus 5 mg daily) without any dose-limiting toxicities. Therefore, per protocol, dose level -1 was defined as the maximum tolerated dose.

| Toxicity | Maximum Grade | | | |
|---------------------|---------------|----|----|----|
| | G1 | G2 | G3 | G4 |
| Febrile neutropenia | - | - | 1 | - |
| Neutropenia | 1 | - | - | - |
| Thrombocytopenia | 3 | 1 | 1 | - |

Hematologic toxicities (see table above) included febrile neutropenia (11%), neutropenia (11%), thrombocytopenia (56%), and anemia (36%). Grade 3 febrile neutropenia and thrombocytopenia each occurred in 1 patient. Non-hematologic toxicities were varied, though many were expected based on the known toxicities of everolimus and pazopanib. One patient did experience a grade 3 pneumothorax, which was possibly related to study therapy. Other non-hematologic toxicities included anorexia (11%), bone pain (11%), diarrhea (22%, 11% G3), fatigue (56%), dysgeusia (11%), headache (11%), hypertension (22%), mucositis (33%), musculoskeletal (muscle stiffness after prolonged periods of sitting, 11%), nausea (44%), palmo-plantar erythrodysesthesia syndrome (11%), pneumonia (11% G3), pruritus (11% G3), rash (33%, 11% G3), vomiting (33%), and weight loss (11%). Toxicities noted in laboratory evaluations were generally consistent with what is expected with both agents administered separately. G3 and 4 laboratory toxicities included increased ALT, hypophosphatemia, and hypouricemia each in 1 patient, and increased lipase in 2 patients.

Treatment was generally well tolerated at the MTD. Two of 6 patients came off treatment after 2 cycles because of toxicity. The others stopped treatment due to disease progression or physician decision.

Antitumor activity

Encouraging antitumor activity was noted in the bladder cancer patients treated on pazopanib and everolimus. Of five urothelial cancer patients evaluable, 3 had stable disease for 4 months, 4 months and 5.5 months respectively. One patient had a complete response which lasted 14 months.

| Tumor type | (n) | Best objective response |
|------------|-----|-------------------------|
|------------|-----|-------------------------|

| | | |
|---------------------------|------------|-----------------|
| Bladder | 5 | 3 SD, 1CR, 1 NE |
| Lung small cell carcinoma | 3 | 2 SD, 1 PD |
| Adrenocortical carcinoma | 1 | 1 SD |
| Median Age (range) | 59 (49-77) | |

SD: stable disease; NE: not evaluable; CR: complete response; PR: partial response; PD: progressive disease.

Based on these findings of preliminary increased activity of the regimen in at least a subset of urothelial carcinoma patients, the protocol is being amended to accrue urothelial carcinoma patients rather than kidney cancer patients in the expansion cohort given the significant unmet need in urothelial carcinoma. Since there are no approved treatments for patients with progressive disease after front-line cytotoxic chemotherapy, testing novel approaches is rational. Metastatic urothelial carcinoma patients treated with 1-3 prior regimens of systemic chemotherapy including at least a platinum agent, a taxane, or gemcitabine will be enrolled. No prior VEGF receptor or mTOR pathway inhibitors are allowed. Patients will continue therapy until progression or unacceptable toxicity.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria for the Dose Escalation cohort

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Phase I: Participants must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective (or who are intolerant of such therapy).

3.1.2 Age \geq 18 years.

3.1.3 Life expectancy of greater than 3 months.

3.1.4 ECOG performance status \leq 1 (Karnofsky \geq 70%, see Appendix A).

3.1.5 Participants must have normal organ and marrow function as defined below:

- Leukocytes \geq 3,000/ mm³
- Absolute neutrophil count \geq 1,500/mm³
- Platelets \geq 100,000/ mm³

- Hemoglobin ≥ 9 g/dL; subjects may not have had an RBC transfusion within 7 days of screening assessment.
- Total bilirubin ≤ 1.5 X normal institutional limits
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min for subjects with creatinine levels about institutional normal
- Partial thromboplastin time (PTT) ≤ 1.5 X institutional ULN unless patients are on therapeutic anticoagulation with warfarin
- Urine protein to urine creatinine ratio (UPC) < 1.0 . 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
- Total cholesterol ≤ 300 mg/dL AND fasting triglycerides ≤ 2.5 x institutional ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

3.1.6 Able to swallow oral medications

3.1.7 Resolution of any pre-existing toxicity from prior therapy to NCI CTCAE V4.0 grade 1 except neuropathy (\leq grade 2) and tinnitus (\leq grade 2), and hearing loss (\leq grade 4)

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

3.1.8.1 Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)
- A bilateral tubal ligation
- Is post-menopausal

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

Subjects must discontinue HRT prior to study enrollment due to the potential for inhibition of CYP enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female subject is determined not to be post-menopausal, they must use adequate contraception as defined immediately below during the trial and for 8 weeks after the last dose.

3.1.8.2 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. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

Note: Oral contraceptives are not reliable due to potential drug-drug interactions.

3.1.8.3 Female subjects who are lactating should not be included in the trial. 3.1.8.4 A male with a female partner of childbearing potential is eligible to enter and participate in the study if he uses a barrier method of contraception or abstinence during the study.

3.1.9 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.

3.2 Exclusion Criteria for the Dose Escalation Cohort

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the dose escalation cohort of this study.

3.2.1 Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Current treatment with leuprolide or other GnRH agonists is permitted on the Phase I portion of the study.

3.2.2 Participants may not be receiving any other study agents during the study or within 4 weeks of the start of the trial.

- 3.2.3** Prior everolimus or pazopanib therapy. Other mTOR inhibitors and tyrosine kinase inhibitors are allowed.
- 3.2.4** 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 weeks prior to the 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. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants will not be allowed. Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.
- 3.2.5** Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or everolimus (such as sirolimus or temsirolimus)
- 3.2.6** Patients who have any severe and/or uncontrolled medical conditions such as:
- Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to start of everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
 - Symptomatic congestive heart failure of New York heart Association Class III or IV
 - Active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
 - Known severely impaired lung function (e.g spirometry and DLCO 50% or less of normal and O₂ saturation 88% or less at or less at rest on room air),
 - Active, bleeding diathesis;
- 3.2.7** Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥ 140 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg]. Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Blood pressure must be re-assessed on two occasions that are separated by a minimum of 24 hours. The mean SBP / DBP values from each blood pressure assessment must be $< 140/90$ mmHg in order for a subject to be eligible for the study.
- 3.2.8** History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Subjects with recent DVT

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

- 3.2.9** Prior major surgery (required as defining general anesthesia) or trauma within 28 days prior to first dose of study drug, and/or not recovered from effects of that surgery, and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major), or patients that may require surgery during the course of the study.
- 3.2.10** Evidence of active bleeding or bleeding diathesis.
- 3.2.11** Known endobronchial lesions or involvement of large pulmonary vessels by tumor
- 3.2.12** Hemoptysis within 6 weeks of first dose of study drug.
- 3.2.13** Use of an investigational agent, including an investigational anti-cancer agent, within 4 weeks, whichever is longer, prior to the first dose of study drug.
- 3.2.14** Clinically significant gastrointestinal abnormalities that may increase the risk for GI bleeding including, but not limited to:
- A. Active peptic ulcer disease
 - B. Known intraluminal metastatic lesion/s with suspected bleeding
 - C. Inflammatory bowel disease
 - D. Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
 - E. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.
- 3.2.15** “Currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy more than 3 years ago and are considered to have a less than 30% risk of relapse based on the enrolling investigator’s assessment and documented in the medical record. A history of prostate cancer that was identified incidentally following cystoprostatectomy or cystectomy for bladder cancer is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower; Gleason score ≤ 7 , negative margins at surgery, and PSA undetectable after surgery.
- 3.2.16** Presence of uncontrolled infection
- 3.2.17** Liver disease such as chronic cirrhosis, active hepatitis, or chronic and persistent hepatitis
- 3.2.18** Uncontrolled diabetes mellitus as defined by HbA1c $>8\%$ despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary;

3.2.19 Current treatment on another clinical trial

3.2.20 Pregnant or breastfeeding. Pregnant women are excluded from this study because pazopanib and everolimus are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with either of these agents, breastfeeding should be discontinued if the mother is treated with either pazopanib or everolimus. These potential risks may also apply to other agents used in this study.

3.2.21 Chronic treatment with systemic corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed. Patient is unable or unwilling to discontinue predefined prohibited medications listed in the protocol for 4 weeks of a drug (whichever is longer) prior to Visit 1 and for the duration of the study.

3.2.22 Treatment with strong CYP3A4 inhibitors:

- Cardiovascular: verapamil and diltiazem
- Antibiotics: clarithromycin, telithromycin, troleandomycin, erythromycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone

3.2.23 Other prohibited medications :

- Oral hypoglycemics: tolbutamide, chlorpropamide
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- Neuroleptics: pimozide
- Antiarrhythmics: amiodarone, bepridil, flecainide, lidocaine, mexilitine, quinidine, propafenone
- Immune modulators: cyclosporine, tacrolimus, sirolimus.
- Miscellaneous: theophylline, quetiapine, risperidone, tacrine, clozapine, atomoxetine

3.2.24 Treatment with strong CYP3A4 inducers:

- Anticonvulsants: phenytoin, carbamazepine, Phenobarbital, oxcarbazepine
- HIV antiretrovirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

- 3.2.25** Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;
- 3.2.26** Prolongation of corrected QT interval (QTc) > 480 msec.
- 3.2.27** History of malabsorption syndrome, disease significantly affecting gastrointestinal function or major resection of stomach or small bowel that could interfere with absorption, distribution, metabolism, or excretion of study drugs.
- 3.2.28** Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity. Hypothyroidism treated with medication is not excluded if TSH is within normal limits.
- 3.2.29** Any serious and/or unstable pre-existing medical, psychiatric, or other condition (including lab abnormalities) that could interfere with subject safety, obtaining informed consent or compliance to study procedures. Examples of such include uncontrolled diabetes, nonhealing wound, severe or uncontrolled infection, severe malnutrition, severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O₂ saturation that is 88% or less at rest on room air, ventricular arrhythmias, active ischemic heart disease, chronic liver or renal disease, or active upper GI tract ulceration.
- 3.2.30** HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib and everolimus. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.
- 3.2.31** Patients unwilling or unable to comply with protocol therapy, tests, and visits, or with a history of noncompliance with medical regimens.

3.3 Eligibility Criteria for the expansion cohort in urothelial carcinoma

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from

the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Participants must meet the following criteria on screening examination to be eligible to participate in the expansion cohort of this study:

- 3.3.1** Metastatic or locally advanced unresectable urothelial carcinoma with histologic or cytologic confirmation at DFCI or MSKCC.
- 3.3.2** Participants must have measurable disease, as defined by RECIST v1.1.
- 3.3.3** Previously treated with at least one and not more than 3 lines of systemic chemotherapy including at least one of the following: a platinum agent, a taxane, or gemcitabine.
- 3.3.4** Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of pazopanib as an anti-cancer agent in patients <18 years of age, children are excluded from this study but may be eligible for future pediatric trials.
- 3.3.5** Life expectancy of greater than 3 months.
- 3.3.6** Karnofsky $\geq 70\%$ or ECOG ≤ 1 (see Appendix A).
- 3.3.7** Participants must have normal organ and marrow function as defined below:
 - WBC $\geq 3,000/\text{mm}^3$
 - Absolute neutrophil count $\geq 1,500/\text{mm}^3$
 - Platelets $\geq 100,000/\text{mm}^3$
 - Hemoglobin ≥ 9 g/dL; subjects may not have had an RBC transfusion within 7 days of screening assessment.
 - Total bilirubin $\leq 1.5 \times$ normal institutional limits
 - AST (SGOT)/ALT (SGPT) $\leq 2.5 \times$ institutional upper limit of normal
 - Creatinine clearance ≥ 40 mL/min
 - Prothrombin time (PT) or international normalized ratio (INR) $\leq 2 \times$ institutional upper limit of normal (ULN) unless patients are on therapeutic anticoagulation with warfarin
 - Partial thromboplastin time (PTT) $\leq 1.5 \times$ institutional ULN unless patients are on therapeutic anticoagulation with warfarin
 - Urine protein to urine creatinine ratio (UPC) < 1.0 . 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

- Total cholesterol ≤ 300 mg/dL AND fasting triglycerides $\leq 2.5 \times$ institutional ULN.
NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

3.3.8 Able to swallow oral medications

3.3.9 Resolution of any pre-existing toxicity from prior therapy to NCI CTCAE V4.0 grade 1 except neuropathy (\leq grade 2) and tinnitus (\leq grade 2), and hearing loss (\leq grade 4)

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

3.3.10.1 Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)
- A bilateral tubal ligation
- Is post-menopausal

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

Subjects must discontinue HRT prior to study enrollment due to the potential for inhibition of CYP enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female subject is determined not to be post-menopausal, they must use adequate contraception as defined immediately below during the trial and for 8 weeks after the last dose.

NOTE: Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

3.3.10.2 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. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

Note: Oral contraceptives are not reliable due to potential drug-drug interactions.

3.3.10.3 A male with a female partner of childbearing potential is eligible to enter and participate in the study if he uses a barrier method of contraception or abstinence during the study and for 8 weeks after the end of treatment.

3.3.11 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.

3.4 Exclusion Criteria for the Expansion Cohort

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

- 3.4.1** Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
- 3.4.2** Participants may not be receiving any other study agents during the study or within 4 weeks of the start of the study.
- 3.4.3** Prior mTOR pathway inhibitor or VEGF receptor inhibitor therapy.
- 3.4.4** 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 weeks prior to the 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.
- Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.
- Anticonvulsants will not be allowed.
- Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.

3.4.5 Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or everolimus (such as sirolimus or temsirolimus)

3.4.6 Any serious and/or unstable pre-existing medical, psychiatric, or other condition (including lab abnormalities) that could interfere with subject safety, obtaining informed consent or compliance to study procedures.

- a. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to start of everolimus, serious uncontrolled cardiac arrhythmia, ventricular arrhythmias, active ischemic heart disease, or any other clinically significant cardiac disease,
- b. Symptomatic congestive heart failure of New York heart Association Class III or IV
- c. Active (acute or chronic) or uncontrolled severe infection
- d. Liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV- RNA)
- e. Known severely impaired lung function (e.g. spirometry and DLCO 50% or less of normal and O₂ saturation 88% or less at rest on room air) active, bleeding diathesis
- f. Severe or uncontrolled infection, severe malnutrition
- g. Chronic renal disease
- h. Active upper GI tract ulceration

- 3.4.7** Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥ 140 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg]. Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Blood pressure must be re-assessed on two occasions that are separated by a minimum of 5 minutes. The mean SBP / DBP values from each blood pressure assessment must be $< 140/90$ mmHg in order for a subject to be eligible for the study.
- 3.4.8** History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
- Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible
- 3.4.9** Prior major surgery (required as defining general anesthesia) or trauma within 28 days prior to first dose of study drug, and/or not recovered from effects of that surgery, and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major), or patients that may require surgery during the course of the study.
- 3.4.10** Evidence of active bleeding or bleeding diathesis.
- 3.4.11** Known endobronchial lesions or involvement of large pulmonary vessels by tumor
- 3.4.12** Hemoptysis within 6 weeks of first dose of study drug.
- 3.4.13** Use of an investigational agent, including an investigational anti-cancer agent, within 4 weeks, whichever is longer, prior to the first dose of study drug.
- 3.4.14** Clinically significant gastrointestinal abnormalities that may increase the risk for GI bleeding including, but not limited to:
- Active peptic ulcer disease
 - Known intraluminal metastatic lesion/s with suspected bleeding
 - Inflammatory bowel disease
Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
- 3.4.15** History of another malignancy within 3 years, except the following: cured basal/squamous cell carcinoma of the skin, excised carcinoma in situ of the cervix. A history of prostate cancer that was identified incidentally following cystoprostatectomy or cystectomy for bladder cancer is acceptable provided that the following criteria are met: Stage T2N0M0 or lower, gleason score ≤ 7 , negative margins at surgery, and PSA undetectable after surgery.

- 3.4.16** Liver disease such as chronic cirrhosis, active hepatitis or chronic persistent hepatitis
- 3.4.17** Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
- 3.4.18** Current treatment on another clinical trial within one month prior to dosing.
- 3.4.19** Pregnant or breastfeeding. Pregnant women are excluded from this study because pazopanib and everolimus are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with either of these agents, breastfeeding should be discontinued if the mother is treated with either pazopanib or everolimus. These potential risks may also apply to other agents used in this study.
- 3.4.20** Chronic treatment with systemic corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- 3.4.21** Patient is unable or unwilling to discontinue predefined prohibited medications listed in the protocol for 4 weeks of a drug or 5 times the half life of a drug (whichever is longer) prior to Visit 1 and for the duration of the study.
- 3.4.22** Treatment with strong CYP3A4 inhibitors:
- Cardiovascular: verapamil and diltiazem
 - Antibiotics: clarithromycin, telithromycin, troleandomycin, erythromycin
 - HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
 - Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
 - Antidepressants: nefazodone
- 3.4.23** Other prohibited medications :
- Oral hypoglycemics: tolbutamide, chlorpropamide
 - Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
 - Neuroleptics: pimozide
 - Antiarrhythmics: amiodarone, bepridil, flecainide, lidocaine, mexilitine, quinidine, propafenone
 - Immune modulators: cyclosporine, tacrolimus, sirolimus.
 - Miscellaneous: theophylline, quetiapine, risperidone, tacrine, clozapine, atomoxetine

3.4.24 Treatment with strong CYP3A4 inducers:

- Anticonvulsants: phenytoin, carbamazepine, Phenobarbital, oxcarbazepine
- HIV antiretrovirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

3.4.25 Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;

3.4.26 Prolongation of corrected QT interval (QTc) > 480 msec.

3.4.27 History of malabsorption syndrome, disease significantly affecting gastrointestinal function or major resection of stomach or small bowel that could interfere with absorption, distribution, metabolism, or excretion of study drugs.

3.4.28 Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity. Hypothyroidism treated with medication is not excluded if TSH is within normal limits.

3.4.29 Any serious and/or unstable pre-existing medical, psychiatric, or other condition (including lab abnormalities) that could interfere with subject safety, obtaining informed consent or compliance to study procedures.

3.4.30 HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib and everolimus. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

3.4.31 Patients unwilling or unable to comply with protocol therapy, tests, and visits, or with a history of noncompliance with medical regimens.

3.4.32 Female subjects who are pregnant or lactating are not eligible to participate in this study.

3.4.32 Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment

3.5 Inclusion of Women, Minorities and Other Underrepresented Populations

Women, minorities, and other underrepresented populations are all eligible for this trial.

Screening for hepatitis B

Prior to randomization/start of everolimus, patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab.

The management guidelines, in Section 6.2.4 are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for hepatitis C

Patients should be tested for hepatitis C using quantitative RNA-PCR.

The management guidelines, in Section 6.2.4 are provided according to the results of the baseline assessment of hepatitis C viral load.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM **Eastern Standard Time**. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.
5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Study Coordinator and research Nurse. All sites should call the Study Coordinator and research Nurse to verify treatment availability.

Following registration, participants should begin protocol treatment within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Study Coordinator should be notified of participant status changes as soon as possible.

Except in very unusual circumstances, each participating institution will order the study agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for pazopanib and everolimus are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy other than described in the inclusion/exclusion criteria.

Phase I dose escalation schema

| | Dose Level | Pazopanib | Everolimus |
|-----------------------|------------|--------------|-------------|
| | -1 | 400 mg PO QD | 5 mg PO QD |
| Starting dose→ | 0 | 600 mg PO QD | 5 mg PO QD |
| | +1 | 600 mg PO QD | 10 mg PO QD |
| | +2 | 800 mg PO QD | 10 mg PO QD |
| | +2A | 800 mg PO QD | 5 mg PO QD |

* Dose level +2A is only to be used if the MTD is exceeded on dose level +2.

5.1 Expansion Cohort

The dose for the expansion cohort is listed below:

| Agent | Dose | Route | Schedule | Cycle Length |
|------------|--------|-------|----------|----------------------|
| Pazopanib | 400 mg | Oral | Daily | 28 days (4 weeks) |
| Everolimus | 5 mg | Oral | Daily | |

5.2 Pre-treatment Criteria

5.2.1 Screening evaluation

Within 28 days prior to start of treatment

- Complete physical examination
- Complete medical history and demographics
- Karnofsky or ECOG performance status
- Record concomitant medications
- Disease assessments: Baseline CT or MRI of the abdomen and pelvis and CT or X-ray of the chest. In patients with osseous lesions, bone X-rays and/or bone scans should be obtained.

Within 14 days prior to start of treatment

- Evaluation of vital signs including pulse, respiratory rate, body weight, and height
- Two blood pressure measurements should be taken at least 5 minutes apart
- Urine beta-HCG pregnancy test for women of childbearing potential
- Electrocardiogram

- Urinalysis, urine protein, and urine creatinine
- Laboratory assessments. Screening laboratory testing performed within 7 days of initiation of study therapy may be used for cycle 1 day 1.
 - Complete blood count with differential and platelets
 - Comprehensive Metabolic Panel including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin
 - Magnesium, phosphorus, LDH, amylase, lipase, thyroid stimulating hormone
 - Total cholesterol ≤ 300 mg/dL AND fasting triglycerides $\leq 2.5 \times$ institutional ULN.
 - Fasting lipid panel
 - Screening for hepatitis C (using quantitative RNA-PCR) and hepatitis B using serological markers (HBsAg, HBsAb, and HBcAb) for all patients.
 - Prothrombin time (PT) or international normalized ratio (INR) $\leq 2X$ institutional upper limit of normal (ULN) unless patients are on therapeutic anticoagulation with warfarin
 - Partial thromboplastin time (PTT) $\leq 1.5 \times$ institutional ULN unless patients are on therapeutic anticoagulation with warfarin

5.2.1 Day 1 every cycle

The following will be undertaken prior to initiating study therapy and on day 1 of every subsequent cycle:

- Vital signs including blood pressure, pulse, respiratory rate and body weight. Height will be recorded on cycle 1, day 1 only.
- Karnofsky or ECOG performance status
- Complete physical examination and toxicity evaluation (CTCAE v 4.0)
- Update concomitant medications
- Complete blood count with differential and platelets
- Comprehensive Metabolic Panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin
- Magnesium, phosphorous, LDH, amylase, lipase, thyroid stimulating hormone
- Fasting lipid panel
- Urine pregnancy test in women of childbearing potential (at screening and cycle 1 day 1 only)
- Urinalysis
- Urine protein & creatinine
- EKG (for cycles 1-2 only)

5.2.2 Cycles 1-2 day 15

The following will be undertaken day 15 of cycles 1 and 2:

- Vital signs including blood pressure, pulse, respiratory rate, body weight, and height
- Karnofsky or ECOG performance status
- Complete physical examination and toxicity evaluation (CTCAE v 4.0)
- Update concomitant medications
- Complete blood count with differential and platelets
- Comprehensive Metabolic Panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin
- Magnesium, phosphorous, LDH

5.2.4 Every 8 weeks

Radiologic disease evaluation: Radiological assessments include a CT or X-ray of the chest and abdominal and pelvic CT or MRI scan. In patients with osseous lesions, bone X-rays and/or bone scans should be obtained. Tumor measurements should occur every 8 weeks (within 7 days prior to day 1 of the subsequent cycle).

5.2.5 End of Study

The following will be undertaken 28 days after last dose of study medication:

- Vital signs including blood pressure, pulse, respiratory rate, body weight, and height
- Karnofsky or ECOG performance status
- Complete physical examination and toxicity evaluation (CTCAE v 4.0)
- Update concomitant medications
- Complete blood count with differential and platelets
- Comprehensive Metabolic Panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin
- Magnesium, phosphorous, LDH, thyroid stimulating hormone
- Fasting lipid panel
- Urinalysis
- Urine protein & creatinine

This visit can be foregone for patients who are too unwell to attend or for other reasons at the investigators discretion. Patients may be contacted thereafter by phone to assess resolution of toxicities, and may be contacted for survival follow up.

5.3 Agent Administration

Pazopanib and everolimus may be taken at the same time. Patients will be instructed to take the everolimus AND Pazopanib at the same time every morning, without food, at least one hour before or two hours after a meal. Before discharge from the clinic, subjects

will be given a study dosing diary to take home. The subject will be instructed to record the date and time that each dose of pazopanib and everolimus is self administered. Study diaries will be reviewed and collected at each visit during the remainder of the study.

5.3.1 Pazopanib

Pazopanib will be self administered (by the patients themselves). Pazopanib will be administered orally as once daily dose continuously from study day 1 until progression of disease or unacceptable toxicity. 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. Dietary habits around the time of pazopanib intake should be as consistent as possible throughout the study. 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.

5.3.2 Everolimus

Dosing regimen

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

Everolimus should be administered orally once daily at the same time every day, without food, at least one hour before or two hours after a meal, at the same time as the Pazopanib. 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.

Tablets

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose.

5.4 Definition of Dose-Limiting Toxicity

5.4.1 Dose escalation rules

General rules:

- Initial dose is dose level 0 for this trial
- All patients in a dose cohort will complete 28 days (1 cycle) of combination treatment prior to the treatment of any patient at a higher dose level.
- If a patient does not complete the 28 days of treatment for reasons that are clearly not adverse events related to treatment, then that patient will be replaced, up to three per dose level.
- If more than three patients need to be replaced on a dose level, then the reasons will be re-evaluated before continuing.
- There will be no inpatient dose escalation.
- To determine that a subject has received study treatment without experiencing DLT, the subject must have missed no more than 5 days of dosing during cycle 1, either nonconsecutively or consecutively.

Pazopanib and everolimus doses will be escalated according to the following standard 3+3 dose escalation rules:

1. If 0 of 3 patients in a cohort experience dose limiting toxicities, then the next cohort of 3 patients will be treated at the next higher dose level.
2. If 1 of 3 patients in a cohort experiences a DLT then the cohort will be expanded to treat an additional three patients. If only one of 6 patients experiences a DLT, then the next cohort of patients will be treated at the next higher dose level.
3. If two or more patients in a cohort experience a DLT, then the MTD has been exceeded. The previous dose level will be considered the MTD. If only 3 patients were treated at the previous dose level, an additional three patients will be treated at that dose level to confirm the MTD.
4. If the doses of both drugs are escalated to dose level 2 with 0 of 3 or 1 out of 6 patients experiencing a DLT, then this will be considered the recommended Phase II dose (RP2D) for the expansion cohort.
5. If the MTD is exceeded on dose level 0, then a de-escalation cohort to dose level -1 will be enrolled. Up to six patients will be treated at this dose level. If one or fewer of six patients experiences a DLT, then this will be the RP2D. If two or more patients experience a DLT on dose level -1, then the combination will be deemed not feasible and the study will be closed.
6. If the MTD is exceeded on dose level 2, then a de-escalation level will be accrued (dose level 2A). If 0 of 3 or 1 out of 6 patients experience a DLT on dose level 2A,

then this will be considered the RP2D for the expansion cohort. If the MTD is exceeded on dose level 2A, then dose level 1 will be the RP2D.

5.4.2 Definition of a DLT

Dose-limiting toxicity (DLT) is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0).

For the purposes of Phase I dose escalation, a DLT will be defined as toxicity occurring within the first 28 days of combination therapy related to therapy that meets the criteria spelled out below:

1. Grade 3 or 4 non-hematologic toxicity excluding:
 - Toxicity attributed to underlying malignancy
 - Nausea/vomiting controlled with antiemetics
 - Grade 3 hypertension that resolves to $\leq 150/90$ within 7 days of adjustment or addition of oral blood pressure medications.
 - a. Hypertension that requires admission to the hospital or intravenous medication for control will be considered a DLT.
 - b. Grade 3 or greater hypertension that does not respond to adjustment or addition of oral blood pressure medicines to $\leq 150/90$ within 7 days from blood pressure medication modification will be considered a DLT.
 - Grade 3 asymptomatic, clinically insignificant laboratory abnormalities, including LDH, alkaline phosphatase due to bone metastases, and asymptomatic hypophosphatemia
2. Hematologic toxicity defined as:
 1. Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding
 2. Grade 4 neutropenia which persists for >7 days
 3. Grade 4 neutropenia associated with fever $>38.5^{\circ}\text{C}$
 4. Excludes lymphopenia or anemia of any grade
3. Removal of a patient from therapy due to toxicity attributable to treatment
4. Patients who miss more than 5 days of the planned doses for drug-related intolerable grade 2 toxicity will be considered to have experienced a DLT. During cycle 1, patients who miss fewer than 5 days of dosing for drug-related toxicities that do not immediately meet the criteria for DLT must recover to \leq grade 1 within two weeks, or they will be considered to have experienced DLT.
5. Toxicity related to therapy severe enough to require a dose-reduction

Management and dose modifications associated with the above adverse events are outlined in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications).

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Patients should receive full supportive care, including analgesic medication, transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Although acetaminophen at doses of ≤ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. The reason(s) for treatment, dosage, and the dates of treatment should be recorded in the medical record.

5.5.2 Palliative radiation therapy may not be administered while the patient is on study treatment. A symptomatic lesion or one which may produce disability (e.g., unstable femur) may be irradiated before study initiation, provided other measurable or evaluable disease is present and radiation therapy is completed ≥ 4 weeks before start of therapy. All eligibility criteria for progression must still be met. Any other indications for radiotherapy after protocol treatment has begun will constitute disease progression, and the patient will stop protocol treatment.

5.5.3 Erythropoietin/ Darbepoetin: Use of erythropoietin or darbepoetin in this protocol is permitted at the discretion of the treating physician after cycle 1 (ie., after the DLT determination period).

5.5.4 Filgrastim (G-CSF), pegfilgrastim, and sargramostim (GM-CSF) after cycle 1 (ie. After the DLT determination period)

1. Filgrastim/pegfilgrastim and sargramostim should not be used to avoid dose reductions.
2. Filgrastim, pegfilgrastim, or sargramostim, may be used for secondary prophylaxis following an episode of febrile neutropenia.
3. For the treatment of febrile neutropenia, the use of CSF's should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSF's may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF (filgrastim, pegfilgrastim or sargramostim) must be documented and reported in the medical record.
4. If filgrastim, pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

5.5.5 Drug Interactions

Because there is a potential for interaction of pazopanib and Everolimus with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator (or

Protocol Chair) should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.5.5.1 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 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.

5.5.5.2 Permitted Medications – Use with Caution

- **Specific recommendations regarding anticoagulants:**

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.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The co-administration of everolimus and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

- **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.

- **Specific recommendations regarding oral hypoglycemics:** Co-administration of pazopanib with some oral hypoglycemics, including glipizide, glyburide (glibenclamide), glimepiride, nateglinide, repaglinide, gliclazide, acetohexamide, carbutamide, glibornuride, glymidine, metahexamide, and tolazamide, may result in an increase in plasma concentrations of the oral hypoglycemic agent. This increase may result in hypoglycemia. Therefore, the dose of the oral hypoglycemic agent should be reduced by 50% when pazopanib administration starts. The blood glucose should be monitored closely, and the subject should be instructed to measure their blood glucose if they experience symptoms of hypoglycemia and inform their physician if their blood glucose concentration is low. After at least 14 days of pazopanib administration, the dose of the oral hypoglycemic agent may be increased as necessary to maintain adequate blood glucose control.
- **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 a weak 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 certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. 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)
 - Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)

- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.
- **The Effects of Other Drugs on Pazopanib and Everolimus**
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**. Competitive inhibition could occur when everolimus is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- 1. Concurrent administration of everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of everolimus).
- 2. Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided. In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.

5.5.5.3 Prohibited Medications

Participants must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the participant to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

- 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.
- No chronic treatment with systemic steroids or other immunosuppressive agents are allowed. Topical or inhaled corticosteroids are allowed.
- Medications that inhibit strongly CYP3A4 may result in increased plasma pazopanib and everolimus concentrations. Selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is required. **Strong CYP3A4 inhibitors which are prohibited include:**

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone
- **Specific recommendation regarding non-dihydropyridine calcium channel blockers (verapamil and diltiazem)**: co-administration of pazopanib with calcium channel blockers may result in increased plasma concentrations of the calcium channel blocker. Non-dihydropyridine calcium channel blockers, verapamil and diltiazem, have potential depressive effects on cardiac conduction and contractility. When pazopanib therapy is initiated, the administration of an anti-hypertensive or anti-anginal agent other than verapamil and diltiazem is recommended in the setting of a prolonged PR interval (greater than 200 msec), sinus bradycardia (less than 60 beats per minute), or second or third degree heart block, unless the subject has a permanent pacemaker.
- **Strong CYP3A4 inducers** may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is required. **Drugs that induce CYP3A4 and may decrease pazopanib and everolimus 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, carbamazepine, phenobarbital, oxcarbazepine
 - HIV antivirals: efavirenz, nevirapine
 - Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
 - Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with everolimus.

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.7 Duration of Follow Up

Participants will be followed for 30 days after treatment discontinuation or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients may be contacted thereafter by phone to assess resolution of toxicities, and may be contacted for survival follow up.

5.8 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Dr. Mark Pomerantz, at (617) 632-6328 or (617) 632-3353 (page operator).

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) which is available at <http://ctep.cancer.gov/reporting/ctc.html>.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Phase I Dose Escalation Cohort:

Individual patient dose reductions for toxicity will be determined by initial starting dose level in the Phase I dose escalation cohort.

For patients on **dose level -1** there will be 1 dose reduction allowed:

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level -1 | 400 mg PO QD | 5 mg PO QD |
| 1 st dose reduction | 200 mg PO QD | 5 mg PO QOD |

If a patient on dose level -1 requires more than one dose reduction, then the patient will stop study therapy

For patients on **dose level 0** there will be only one dose reduction:

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level 0 | 600 mg PO QD | 5 mg PO QD |
| 1 st dose reduction | 400 mg PO QD | 5 mg PO QOD |

If a patient on dose level 0 requires more than one dose reduction, then the patient will stop study therapy. If a patient has pneumonitis related to everolimus, then pazopanib dose level may be maintained and everolimus dose reduced or discontinued (see Table 6.2.3).

For patients on **dose level +1** there will be 2 dose reductions allowed:

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level +1 | 600 mg PO QD | 10 mg PO QD |
| 1 st dose reduction | 400 mg PO QD | 5 mg PO QD |
| 2 nd dose reduction | 200 mg PO QD | 5 mg PO QOD |

If a patient on dose level +1 requires more than 2 dose reductions, then the patient will stop study therapy. If a patient has pneumonitis related to everolimus, then pazopanib dose level may be maintained and everolimus dose reduced or discontinued (see Table 6.2.3).

For patients on **dose level +2** there will be 2 dose reductions allowed:

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level +2 | 800 mg PO QD | 10 mg PO QD |
| 1 st dose reduction | 600 mg PO QD | 5 mg PO QD |

| | | |
|--------------------------------|--------------|-------------|
| 2 nd dose reduction | 400 mg PO QD | 5 mg PO QOD |
|--------------------------------|--------------|-------------|

If a patient on dose level +2 requires more than 2 dose reductions, then the patient will stop study therapy. If a patient has pneumonitis related to everolimus, then pazopanib dose level may be maintained and everolimus dose reduced or discontinued (see Table 6.2.3).

For patients on **dose level +2A** there will be 2 dose reductions allowed:

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level +2A | 800 mg PO QD | 5 mg PO QD |
| 1 st dose reduction | 600 mg PO QD | 5 mg PO QOD |
| 2 nd dose reduction | 400 mg PO QD | discontinue |

If a patient on dose level +2A requires more than 2 dose reductions, then the patient will stop study therapy. If a patient has pneumonitis related to everolimus, then pazopanib dose level may be maintained and everolimus dose reduced or discontinued (see Table 6.2.3).

Phase I expansion cohort:

Individual patient dose reductions for toxicity will be determined by initial starting dose level in the Phase I expansion cohort which was dose level -1 as per results of the first phase of the study.

For patients on **dose level -1** there will be 1 dose reduction allowed:

Table 6 Dose Expansion cohort: Dose levels.

| Dose Level | Pazopanib | Everolimus |
|--------------------------------|--------------|-------------|
| Starting dose level -1 | 400 mg PO QD | 5 mg PO QD |
| 1 st dose reduction | 200 mg PO QD | 5 mg PO QOD |

If a patient on dose level -1 requires more than one dose reduction, then the patient will stop study therapy. If, however, a patient is deriving benefit from one agent, as displayed by stable disease or better at restaging, and cannot tolerate the other, the patient may continue on monotherapy of the tolerated agent after discussion with the overall PI, Mark Pomerantz, MD. If one agent is discontinued for toxicity, a patient may dose-increase to the standard monotherapy dose (see Table 7) of the other agent after discussion with the overall PI.

Table 7 Standard Monotherapy Dose Levels

| Dose Level | Pazopanib | Everolimus |
|------------|-----------|------------|
|------------|-----------|------------|

| | | |
|---|--------------|-------------|
| Dose level when other agent is discontinued due to toxicity | 800 mg PO QD | 10 mg PO QD |
|---|--------------|-------------|

If a patient has pneumonitis related to everolimus, then pazopanib dose level may be maintained and everolimus dose reduced or discontinued (see Table 6.2.3).

6.1 Anticipated Toxicities

6.1.1 Everolimus

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea. Infections have not been notably frequent or severe. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts, hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia.

Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting so that this aspect must be verified when interpreting results.

Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results.

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, nonmalignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic. Advice on the management of pneumonitis has been provided in Table 6.2.3. In oncology studies with everolimus, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveolar haemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug-related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting everolimus. Cytology for both the pleural and pericardial fluids were positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug. Additionally, one patient treated

with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung. Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with everolimus: mycobacterium, aspergillus, and fatal candidal sepsis, and fatal pneumocystis carinii in particular. Because everolimus, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with everolimus must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections.

A reduction in blood cell counts is frequent when everolimus therapy is initiated. Without clinical significance and infrequently, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, everolimus should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug-related thrombocytopenia.

Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with everolimus in oncology clinical studies, and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminase's (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 ($\leq 2.5 \times$ institution ULN).

Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer.

Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest of the patients had concurrent morbidities, which might have contributed to the reported events.

Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with everolimus.

6.1.2 Pazopanib

The most common adverse events (AEs) reported to date include diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia,

headache, abdominal pain, rash, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE). The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon.

The most common serious adverse events (SAEs) occurring in subjects enrolled in pazopanib studies regardless of treatment assignment include vomiting, diarrhea, abdominal pain, hypertension/hypertensive crisis, dyspnea, pleural effusion, pyrexia, anemia, dehydration, and pulmonary embolism.

Evaluation of the safety and efficacy of pazopanib in advanced RCC subjects include a recently completed Phase II study in subjects with advanced RCC, and a Phase III randomized, double-blind study against placebo which completed enrolment in April, 2007 and is currently on-going. To date, 660 subjects with advanced/metastatic RCC have been enrolled in these two clinical trials. Safety data from the Phase II RCC trial VEG102616 (n=225) are summarized here. The most common AEs (defined as AEs experienced by $\geq 10\%$ of subjects) regardless of causality in decreasing order of frequency were diarrhea (63%), fatigue (46%), hair color change (43%), nausea (42%), hypertension (41%), anorexia (24%), dysgeusia (24%), vomiting (20%), headache (20%), cough (17%), abdominal pain (16%), rash (16%), constipation (15%), ALT elevation (14%), arthralgia (13%), AST elevation (12%), back pain (12%), dizziness (12%), handfoot syndrome (11%), alopecia, (10%), dyspepsia (10%), and peripheral edema (10%). The majority of these events were Grade 1 and 2 with hypertension being observed in 9% of subjects as a Grade 3 event.

The most common hematological toxicities of any grade (graded according to NCI-CTCAE) include lymphopenia (47%), thrombocytopenia (28%), neutropenia (23%), and anemia (26%) with combined Grade 3 and 4 abnormalities occurring in 7%, 3%, <1%, and 4% of subjects, respectively. The most common chemistry abnormality was hyperglycemia, observed in 46% of subjects (of which 2% were Grade 3 and no Grade 4). Hyponatremia of any grade was observed in 37% of subjects, with Grade 3 or Grade 4 hyponatremia in 8% of subjects. Hyperkalemia of any grade was reported in 27% of subjects, with Grade 3 or 4 hyperkalemia in 5% of subjects. Hyponatremia and hyperkalemia have not occurred concurrently in the same subject to indicate adrenal insufficiency. Elevations in amylase and lipase of any grade were reported in 23% and 27% of subjects, respectively, with Grade 3 or Grade 4 events in 4% and 9% of subjects, respectively. There were 2 reports of pancreatitis. Increase in TSH was reported in 28% of subjects and a decrease in thyroxine (T4) in 1% of subjects. Three subjects initiated treatment with thyroid replacement therapy (synthroid or levothyroxine) during the study.

ALT elevations of any Grade were reported in 53% of subjects with Grade 3 and Grade 4 elevations in 9% and <1% of subjects, respectively. AST elevations were reported in 53% of subjects with Grade 3 and Grade 4 elevations in 5% and <1% of subjects, respectively.

Hyperbilirubinemia of any Grade occurred in 28% of subjects with Grade 3 elevations in <1% of subjects. No Grade 4 elevations have been reported. Concomitant elevations in transaminases and bilirubin have been observed in 2 (<1%) subjects. Neither of these patients met the criteria for Hy's rule. Risk factors that may have contributed to the liver dysfunction were identified in some of these subjects, (e.g., large mass at the porta hepatis, hepatotoxic concomitant medications). Liver enzyme elevations were reversible upon dose interruption. Two patterns of transaminase changes have been observed:

- (1) transaminase elevations that declined over time without dose interruption.
- (2) transaminase elevations that declined over time upon dose interruption. In some subjects, elevations in transaminase recurred upon rechallenging and these subjects were permanently discontinued from study treatment.

Serial adrenocorticotrophic hormone (ACTH) stimulation tests were conducted in two Phase I and two Phase II trials in cancer subjects with data available in 47 subjects. Twenty-one of them had data beyond 24 weeks and 5 subjects had data beyond 52 weeks. None of these 47 subjects had adrenal insufficiency.

Certain uncommon AEs with significant clinical consequences reported in pazopanib clinical trials (denominator for total subject enrolment n=1000 used for calculating frequency) include pulmonary embolism (0.6%), venous thrombosis (0.3%), venous thrombosis and pulmonary embolism (0.2%), serious hemorrhage (1.4%), bowel perforation (0.5%), myocardial infarction/angina (0.7%), cerebrovascular accidents/transient ischemia (0.6%), cardiac failure (0.2%), atrial fibrillation (0.3%), renal failure (0.8%) and seizures (0.3%)

6.2 Toxicity Management

All toxicities, both during and after the DLT-determining period will follow the guidelines laid out here in sections 6.2 and 6.3.

For definition of a DLT, refer back to section 5.4.

6.2.1 Management of stomatitis/oral mucositis/mouth ulcers

| Adverse Drug Reaction | Severity | Everolimus Dose Adjustment and Management Recommendations |
|-----------------------|----------|---|
| Stomatitis | Grade 1 | No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day. |
| | Grade 2 | Temporary dose interruption until recovery to grade ≤ 1 . Re-initiate everolimus at same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤ 1 . Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, methol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*. |
| | Grade 3 | Temporary dose interruption until recovery to grade ≤ 1 . Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, methol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*. |
| | Grade 4 | Discontinue everolimus and treat with appropriate medical therapy. |

* using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If the examination reveals mouth ulcers rather than a more general inflammation of the mouth, the adverse event should be classified as mouth ulcers. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids**, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, thereby leading to higher everolimus exposures. Therefore, topical

antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, CTCAE v 4.0. Dose reductions are made according to section 6.3.1 (Non-hematological toxicity) and Section 6.3.3.

6.2.2 Management of hyperlipidemia & hyperglycemia

| Adverse Drug Reaction | Severity | Everolimus Dose Adjustment and Management Recommendations |
|--|----------|---|
| Metabolic events (e.g. hyperglycemia, dyslipidemia) | Grade 1 | No dose adjustment required. Initiate appropriate medical therapy and monitor. |
| | Grade 2 | No dose adjustment required. Manage with appropriate medical therapy and monitor. |
| | Grade 3 | Temporary dose interruption. Re-initiate everolimus at lower dose. Manage with appropriate medical therapy and monitor. |
| | Grade 4 | Discontinue everolimus and treat with appropriate medical therapy. |

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher ($>2.5\times$ upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on everolimus.

6.2.3 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving everolimus therapy. Non-infectious pneumonitis has been associated with everolimus and other mTOR inhibitors (Atkins 2004). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest CT scans may be performed, when clinically necessary. If noninfectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with everolimus should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc). Management of non-infectious pneumonitis suspected to be associated with everolimus and dose modifications instructions are provided in Table 6.2.3.

Table 6.2.3 Management of non-infectious pneumonitis

| Worst grade pneumonitis | Suggested investigations | Management of pneumonitis | everolimus dose adjustment |
|--------------------------------|--|--|--|
| Grade 1 | CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O ₂ saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline. | No specific therapy is required | No dose adjustment required for Pazopanib or everolimus. Initiate appropriate monitoring. |
| Grade 2 | CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1 or baseline. Return to initial monitoring frequency if no recurrence. | Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome. | Rule out infection and consider interruption of everolimus (and optional pazopanib) until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days. Pazopanib may resume at the discretion of the treating physician <u>and</u> principal investigator once toxicity is recovered to ≤ Grade 1 even if everolimus is discontinued. |
| Grade 3 | CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended. | Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. | Rule out infection and interrupt everolimus and pazopanib until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower (approximately 50% lower than the dose previously administered depending on individual clinical circumstances) Discontinue everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation of everolimus. Pazopanib may resume at the discretion of the treating physician <u>and</u> principal investigator once toxicity is recovered to ≤ Grade 1 even if everolimus is discontinued. |
| Grade 4 | CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O ₂ saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible. | Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. | Rule out infection and discontinue everolimus. Pazopanib may resume at the discretion of the treating physician <u>and</u> principal investigator once toxicity is recovered to ≤ Grade 1 even if everolimus is discontinued. |

* A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

6.2.4 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6.2.4.1 provides detail of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 6.2.4.1 Action to be taken based on screening hepatitis B results

| Test | Result | Result | Result | Result | Result |
|----------------|--|--------|---|--------|---|
| HBV-DNA | + | + or - | - | - | - |
| HBsAg | + or - | + | - | - | - |
| HBsAb | + or - | + or - | + and no prior HBV vaccination | + or - | - or + with prior HBV vaccination |
| HBcAb | + or - | + or - | + or - | + | - |
| Recommendation | Prophylaxis treatment should be started 1-2 weeks prior to first dose of everolimus Monitor HBV-DNA approximately every 4-8 weeks | | No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks | | No specific action |

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of everolimus. For HBV reactivation definition and management guidelines, see Table 6.2.4.2

Table 6.2.4.2 Guidelines for the management of hepatitis B reactivation

| HBV reactivation (with or without clinical signs and symptoms)* | |
|--|---|
| <p>For patients with baseline results: Positive HBV-DNA OR positive HBsAg</p> <p>-----</p> <p>reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]</p> | <p>Treat: Start a second antiviral medication AND Interrupt everolimus administration until resolution: 1. \leq baseline HBV-DNA levels</p> <p>If resolution occurs within ≤ 28 days, everolimus should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of everolimus.</p> <p>If resolution occurs > 28 days Patients should discontinue everolimus but continue both antiviral therapies at least 4 weeks after last dose of everolimus.</p> |
| <p>For patients with baseline results: Negative HBV-DNA and HBsAg</p> <p>AND [Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb]</p> <p>-----</p> <p>Reactivation is defined as: New appearance of measurable HBV-DNA</p> | <p>Treat : Start first antiviral medication AND Interrupt everolimus administration until resolution: 2. \leq undetectable (negative) HBV-DNA levels</p> <p>If resolution occurs within ≤ 28 days, everolimus should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of everolimus.</p> <p>If resolution occurs > 28 days Patients should discontinue everolimus but continue antiviral therapy at least 4 weeks after last dose of everolimus.</p> |

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 4–8 weeks for HCV flare:

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to 6.2.4.3

Table 6.2.4.3 Guidelines for the management of hepatitis C flare

| Baseline results | HCV flare definition* | HCV flare management |
|--|--|------------------------|
| Detectable HCV-RNA | > 2 log ₁₀ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher. | Discontinue everolimus |
| Knowledge of past hepatitis C infection with no detectable HCV-RNA | New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher. | Discontinue everolimus |

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

6.2.5 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus. Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

6.2.6 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.3 Dose Modifications/Delays

6.3.1 General dose modification/Delays

Dose modifications for toxicities not otherwise covered in section 6.2 are listed in the table below. Patients who do not recover to grade 2 or less toxicity within 28 days will be removed from protocol therapy except where noted (ie. pneumonitis). In addition, patients may hold study intervention (pazopanib and everolimus) for greater than 28 days if the patient's physician and the overall principal investigator, Mark Pomerantz, MD, agree that the patient is deriving clinical benefit from the study drugs. Dose modifications for specific toxicities are covered in sections 6.2 and 6.3.

All toxicities, both during the DLT period and after it has been completed, will follow the guidelines laid out here in sections 6.2 and 6.3.

For definition of a Dose Limiting Toxicity, refer back to section 5.4.

Non-hematological toxicity

| Toxicity | Actions |
|---|---|
| Non-Infectious Pneumonitis | Please refer to section 6.2.3 |
| Reactivation of HBV or HCV flare | Please refer to section 6.2.4 |
| <u>Non-hematological toxicity</u> Grade 2 (except pneumonitis – refer to section 6.2.3) (except hypertension, proteinuria, venous or arterial thrombosis, QTc prolongation- refer to section 6.3.2) (except hepatotoxicity – refer to section 6.3.3) (except elevated amylase and lipase- refer to section 6.3.5) | If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is “intolerable” to patient, interrupt pazopanib and everolimus until recovery to grade ≤1. Then reintroduce pazopanib and everolimus at same dose. If event returns to “intolerable” grade 2, then interrupt pazopanib and everolimus until recovery to grade ≤1. Then reintroduce pazopanib and everolimus at one dose level lower. If event is recurrent “intolerable” grade 2 despite two dose reductions, discontinue pazopanib and everolimus. |
| Grade 3 or 4 (except hyperlipidemia ¹⁾) (except pneumonitis – refer to section 6.2.3) (except hypertension, proteinuria, venous or arterial thrombosis, QTc prolongation- refer to section 6.3.2) (except hepatotoxicity – refer to section 6.3.3) | Interrupt pazopanib and everolimus until recovery to grade ≤1. Then reintroduce pazopanib and everolimus at one dose level lower. No more than 2 dose reductions allowed. |
| Stomatitis / oral mucositis / mouth ulcers | See section 6.2.3 Management of stomatitis / oral mucositis / mouth ulcers |
| Recurrence of grade 3 toxicity after dose reduction | Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued. |
| | Interrupt everolimus administration until resolution to ≤ grade 1 or baseline |

| | |
|---|---|
| Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.2.2.) | <p>grade / value.</p> <p>If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption.</p> <p>If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus until recovery to \leq grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available.</p> <p>Patients will be withdrawn from the study if they fail to recover to \leq grade 1 or baseline grade / value within 28 days.</p> |
| Any other grade 4 | <p>Hold everolimus until recovery to grade ≤ 1 or baseline value</p> <p>Reintroduce everolimus at one dose level lower, if available.</p> |
| Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma) | Discontinue everolimus and Pazopanib |
| Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction | Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation. |
| Recurrence of grade 4 after dose reduction | Discontinue everolimus and Pazopanib |
| Any non-hematologic toxicity requiring everolimus interruption for > 28 days | Discontinue everolimus and Pazopanib |

¹Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies without dose reduction (see Section 6.2.2).

Hematological toxicity

| | |
|---|--|
| Grade 2 Thrombocytopenia (platelets $<75 -50 \times 10^9/L$) | Interrupt pazopanib and everolimus until recovery to grade ≤ 1 ($\geq 75 \times 10^9/L$). Then reintroduce pazopanib and everolimus at initial dose. If thrombocytopenia again returns to grade 2, interrupt pazopanib and everolimus until recovery to grade ≤ 1 . Then reintroduce everolimus at one dose level lower. No more than two dose reductions are allowed. |
| Grade 3 or 4 Thrombocytopenia (platelets $<50 \times 10^9/L$) | Interrupt pazopanib and everolimus until recovery to grade ≤ 1 (platelets $\geq 75 \times 10^9/L$). Then resume pazopanib and everolimus at one dose level lower. If grade 3 or 4 thrombocytopenia recurs, discontinue pazopanib and everolimus. |
| Grade 1& 2 Neutropenia (neutrophils $\geq 1 \times 10^9/L$) | |
| Grade 3 Neutropenia (neutrophils $<1, \geq 0.5 \times 10^9/L$) | No modification of dose. |

| | |
|---|---|
| Grade 4 Neutropenia (neutrophils $< 0.5 \times 10^9/L$) | <p>Interrupt everolimus and Pazopanib until resolution to grade ≤ 1 or baseline value</p> <p>If AE resolution occurs ≤ 7 days, reintroduce everolimus and pazopanib at the same dose level.</p> <p>If AE resolution occurs > 7 days (within 28 days), reintroduce everolimus and pazopanib at one dose level lower, if available. Discontinue patient from study therapy if recurrent grade 3 or greater neutropenia after two dose reductions.</p> |
| Grade 3 febrile neutropenia (not life-threatening) | <p>Interrupt pazopanib and everolimus until recovery to grade ≤ 1 (neutrophils $\geq 1.5 \times 10^9/L$). Then resume pazopanib and everolimus at one lower dose level. If grade 3 or grade 4 neutropenia occurs despite two dose reductions, discontinue pazopanib and everolimus.</p> |
| Grade 4 febrile neutropenia (life-threatening) | <p>Hold further pazopanib and everolimus until the ANC $\geq 1,500/mm^3$ and fever has resolved and antibiotics are discontinued. Then resume pazopanib and everolimus at one dose level lower. If febrile neutropenia recurs, discontinue pazopanib and everolimus.</p> |
| Any hematological or non-hematological toxicity requiring interruption for ≥ 4 weeks | <p>Discontinue pazopanib and everolimus.</p> <p>Discontinue pazopanib and everolimus</p> |

6.3.2 Management of hypertension, proteinuria, hemorrhage/bleeding, venous and arterial thrombosis, QTc prolongation

| 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 ≥ 20 mmHg. | <p>Step 1. Pazopanib and everolimus at the current dose.</p> <p>Step 2. Adjust current or initiate new antihypertensive medication(s).</p> <p>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 specialist and go to scenario (B).</p> |

| AE Terms & Descriptions | Dose Modification Algorithms |
|--|---|
| (B). Asymptomatic SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A). | <p>Step 1. Interrupt pazopanib and everolimus.</p> <p>Step 2. Adjust current or initiate new antihypertensive medication(s).</p> <p>Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.^a</p> <p>Step 4. Once BP is well-controlled, dose reduce pazopanib and everolimus and restart at one dose level lower.</p> |
| (C). Symptomatic hypertension or recurring SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg, despite modification of antihypertensive medication(s) | <p>Step 1. Interrupt pazopanib and everolimus</p> <p>Step 2. Adjust current or initiate new antihypertensive medication(s).</p> <p>Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP^a. Referral to a specialist for further evaluation and follow-up is also recommended.</p> <p>Step 4. Once BP is well-controlled, dose reduce pazopanib and everolimus and restart at one dose level lower.</p> |
| (D). Refractory hypertension unresponsive to above interventions. | Discontinue pazopanib and everolimus and continue follow-up per protocol. |
| a. Well-controlled BP defined as mean SBP < 140 mmHg and mean DBP < 90 mmHg. | |
| Proteinuria | |
| 24-hr urine protein ≥ 3 grams | <p>Step 1. Interrupt pazopanib and everolimus.</p> <p>Step 2. The 24-hour urine protein will be tested weekly until the level is < 3 grams. Then, restart pazopanib and everolimus dose reduced one dose level.</p> <p>Step 3. If 24-hour urine protein ≥ 3 grams recurs once, repeat Steps 1 and 2.</p> <p>Step 4. If 24-hour urine protein ≥ 3 grams recurs after 2 dose reductions, discontinue pazopanib and everolimus</p> |
| Hemorrhage /Bleeding | |
| Grade 1 | Continue pazopanib and everolimus with current dose; monitor as clinically indicated. |
| Grade 2 | <p>Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and everolimus and continue follow-up per protocol. Otherwise, interrupt pazopanib and everolimus until the AE resolved to \leq Grade 1.</p> <p>Step 2. Restart pazopanib and everolimus; reduce dose by one dose level and consult with study PI, monitor as clinically indicated.</p> |
| Grade 3 or 4, or Recurrent \geq Grade 2 event after | Discontinue pazopanib and everolimus and continue with follow-up per protocol. |

| AE Terms & Descriptions | Dose Modification Algorithms |
|--|--|
| dose interruption/reduction. | |
| Venous Thrombosis (DVT, PE) | |
| Grade 2 | Continue everolimus and pazopanib at the same dose |
| Grade 3 | <p>Step 1. Interrupt pazopanib and everolimus.</p> <p>Step 2. Initiate and monitor anticoagulation as clinically indicated.</p> <p>Step 3. Resume pazopanib and everolimus with one dose reduction only if all of the following criteria are met:</p> <ul style="list-style-type: none"> The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. <p>Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib and everolimus dosing (eg, re-initiating, escalating/de-escalating, or discontinuing pazopanib and everolimus), 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</p> |
| Grade 4 and/or PE | Discontinue pazopanib and everolimus and continue follow-up per protocol. |
| Arterial Thrombosis/Ischemia | |
| Any Grade | Discontinue pazopanib and everolimus 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 $\geq 480 < 500$ msec | Continue pazopanib and everolimus; monitor as clinically indicated. |
| QTc ≥ 500 msec | Discontinue pazopanib and everolimus and continue follow-up per protocol. |

6.3.3 Dose Interruptions/Modifications for Hepatotoxicity

Recommendations for everolimus and pazopanib dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided below. 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.

| Event | Dose Modification Algorithms |
|--|---|
| (A). ALT of $\leq 3.0 \times$ upper limit of normal (ULN) | Continue pazopanib and everolimus at current dose with full panel liver function tests (LFTs) ³ monitored as per protocol. |
| (B). ALT $>3.0 \times$ ULN to $\leq 8.0 \times$ ULN without bilirubin elevation (defined as total bilirubin $<2.0 \times$ ULN or direct bilirubin $\leq 35\%$) and without hypersensitivity symptoms (e.g., fever, rash) ² | <ol style="list-style-type: none"> 1. Continue everolimus and pazopanib at current dose. 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • 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 aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1. |
| (C). ALT $>8.0 \times$ ULN without bilirubin elevation (defined as total bilirubin $<2.0 \times$ ULN or direct bilirubin $\leq 35\%$) and without hypersensitivity symptoms (e.g., fever, rash) ² | <p>1st occurrence</p> <p>Interrupt everolimus and pazopanib until toxicity resolves to \leq Grade 1 or baseline</p> <ol style="list-style-type: none"> 2. Perform the following assessments for excluding hypersensitivity and other contributing factors: <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> • * If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks. Re-challenge may be considered if ALL following criteria are met: <ul style="list-style-type: none"> • ALT/AST reduced to Grade 1 • Total bilirubin $<1.5 \times$ ULN or direct bilirubin $\leq 35\%$ • No hypersensitivity signs or symptoms • Subject is benefiting from therapy. • Pazopanib and everolimus will be decreased by one dose level if treatment resumes. • If AST or ALT elevation is $> 20 \times$ ULN, everolimus should be discontinued if resolution takes > 7 days <p>Recurrence</p> |

| Event | Dose Modification Algorithms |
|--|---|
| | Discontinue everolimus and pazopanib 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). | <ol style="list-style-type: none"> 1. Discontinue everolimus and pazopanib immediately 2. Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: <ul style="list-style-type: none"> • 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. If everolimus |
| For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT < 3 X ULN) | <ol style="list-style-type: none"> 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 > 1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue everolimus and pazopanib at the same dose. If bilirubin is >35% direct (conjugated), stop everolimus and pazopanib and further evaluation for underlying cause of cholestasis should be performed. 3. If the subject is benefiting from the study treatment, contact Principal Investigator for possible re-challenge. Re-treatment may be considered if ALL following criteria are met: <ul style="list-style-type: none"> • ALT < 3X ULN • Total bilirubin <1.5 x ULN or direct bilirubin $\leq 35\%$ • No hypersensitivity signs or symptoms • Subject is benefiting from therapy. Pazopanib and everolimus will be decreased by one dose level if treatment resumes. |

a. ³Full panel LFTs include: AST, ALT, alkaline phosphatase, γ -GT (GGT) and total bilirubin.

² Should HCV flare be confirmed, the guidelines for flare must take precedence (See section 6.2.4)

* Please refer to the Pazopanib Investigator's Brochure, Summary of Data and Guidance for Investigator, Warnings and Precautions, Hepatic Effects for information about rechallenge dose

6.3.4 Dose modifications for elevated amylase and lipase

| Event | Dose Modification Algorithm |
|--|--|
| Grade 2 elevation of amylase and lipase without symptoms of pancreatitis | Monitor amylase and lipase every other week, continue study therapy at the same dose level |

| | |
|--|--|
| Grade 2 elevation of amylase and lipase with symptoms of pancreatitis | Hold study therapy until both labs and symptoms are grade 1 or less. Consider restarting study therapy with a dose reduction if the patient is known to be deriving clinical benefit |
| Grade 3 elevation of amylase and lipase without symptoms of pancreatitis | Check amylase and lipase weekly until grade 2 or less, monitor for symptoms weekly (phone contact or visit) until grade 2 or less, and continue study therapy at the same dose level. Consider GI consultation. |
| Grade 3 elevation of amylase and lipase with symptoms of pancreatitis | Hold study therapy until both laboratory testing and symptoms are grade 1 or less. GI consultation is recommended. Consider restarting study therapy with a dose reduction if the patient is known to be deriving clinical benefit from treatment. |
| Grade 4 elevation of amylase and lipase without symptoms of pancreatitis | Hold study therapy until grade 2 or less, restart with one dose-level reduction if the patient is known to be deriving clinical benefit from treatment. GI consultation recommended. |
| Grade 4 elevation of amylase and lipase with symptoms of pancreatitis | Hold study therapy until both laboratory testing and symptoms are grade 1 or less. GI consultation is recommended. Consider restarting study therapy with a dose reduction if the patient is known to be deriving clinical benefit from treatment. |

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Everolimus

Everolimus will be provided by Novartis. Tablets are blister packed under aluminum foil in units of 10 tablets, which should be opened only at the time of administration, as everolimus is both hygroscopic and light sensitive.

7.1.1 Description

everolimus, an inhibitor of mTOR, is an antineoplastic agent. The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone. The molecular formula is C₅₃H₈₃NO₁₄ and the molecular weight is 958.2.

7.1.2 Form

Everolimus is supplied as tablets for oral administration containing 2.5 mg, 5 mg, 7.5 mg, and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients. Everolimus 5 mg tablet is a white to slightly yellow elongated tablet with beveled edge and no score engraved with “5” on one side and “NVR” on the other. Everolimus 10 mg tablet is a white to slightly yellow elongated tablet with beveled edge and no score engraved with “UHE” on one side and “NVR” on the other side.

7.1.3 Storage and Stability

Store everolimus tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children. Everolimus is both hygroscopic and light-sensitive.

7.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Everolimus tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Study personnel should avoid exposure to crushed tablets.

7.1.5 Compatibility

N/A

7.1.6 Availability

Everolimus is considered an investigational agent in this study and will be supplied free-of-charge from Novartis.

7.1.7 Preparation

N/A

7.1.8 Administration

Patients will be instructed to take the everolimus in the morning, without food, at least one hour before or two hours after a meal, at the same time as the Pazopanib.

7.1.9 Ordering

Everolimus can be ordered from Novartis using a drug order form e-mailed to Novartis.

7.1.10 Accountability

All missed doses must be documented in the drug accountability log and the subject's medical record. Unused agent that is returned by subject is not held, but destroyed according to institutional policy. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent. This should be kept current and contain:

- Dates and quantities of investigational product received from Novartis
- Packaging lot numbers for product received
- Subject's identification
- Date and quantity of investigational product dispensed
- The initials of the dispenser

7.1.11 Destruction and Return

At the end of the study, unused supplies of everolimus should be destroyed according to institutional policies unless otherwise instructed by supplier Novartis. Destruction/return will be documented in the Drug Accountability Record Form.

7.2 Pazopanib

7.2.1 Description

Pazopanib, 5-[[4-[(2,3-Dimethyl-2H=indazol-6-yl)-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride, is an orally bioavailable angiogenesis inhibitor. Its molecular formula is C₂₁H₂₃N₇O₂S•HCl. Excipients in the tablet include microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, and a film-coat.

7.2.2 Form

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
- 400mg, oval-shaped, white, packaged in bottles containing 68 tablets each

7.2.3 Storage and Stability

Pazopanib 200mg and 400mg should be stored up to 25°C. Pazopanib has a 48 month shelf-life.

7.2.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Pazopanib tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Study personnel should avoid exposure to crushed tablets.

7.2.5 Compatibility

N/A

7.2.6 Availability

Pazopanib will be provided by GlaxoSmithKline free of charge.

7.2.7 Preparation

N/A

7.2.8 Administration

Patients will be instructed to take the Pazopanib in the morning, without food, at least one hour before or two hours after a meal, at the same time as the everolimus. The tablets should be swallowed whole and must not be crushed or broken.

7.2.9 Ordering

GlaxoSmithKline will ship labeled pazopanib bottles in a sealed carton (68 tabs per bottle for pazopanib 400mg and 34 tabs per bottle for pazopanib 200mg). A label will be affixed to each carton identifying the product, strength and number of bottles. In addition, a packing slip will be enclosed with the drug name, strength, lot/batch number, storage conditions, and expiration/retest date.

7.2.10 Accountability

All missed doses must be documented in the subject's medical record and patient diary. Unused agent that is returned by subject is not held, but destroyed according to institutional policy. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent. This should be kept current and contain:

- Dates and quantities of investigational product received from GlaxoSmithKline
- Packaging lot numbers for product received
- Subject's identification
- Date and quantity of investigational product dispensed
- The initials of the dispenser
- Dose preparation records

7.2.11 Destruction and Return

At the end of the study, unused supplies of Pazopanib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies

Phase I: Patients will have pharmacokinetic specimens drawn at 0, 1, 2, 4, 6 and 24 hours post-dose on cycle 1 days 1 and 15. If patients are treated on dose level -1, there will be a 48 hour blood draw (pre-dose) as well. Two samples will be drawn for each time point. Pharmacokinetic specimens should be collected as close to the indicated window as possible. Whole blood samples (2 mL) should be collected in EDTA vacutainers for everolimus pharmacokinetics. Whole blood samples for the determination of plasma pazopanib concentrations will be collected into separate 2mL EDTA vacutainers. The 24 hour pharmacokinetic specimen should be collected prior to drug dosing on day 2 and day 16. If patients are treated on dose level -1, there will be an additional 48-hour post-dose blood draw obtained prior to everolimus dose. In addition, two 2mL blood samples for everolimus and pazopanib concentration determination will be obtained cycle 2 day 1 and cycle 4 day 1.

Testing will be done on whole blood including plasma. See Appendices B and C for details on blood specimen procurement and shipping.

Expansion Cohort: Pharmacokinetic studies will not be performed in the expansion cohort

9. STUDY CALENDAR

Scans must be done ≤ 4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

9.1 Phase I:

| | | Treatment cycles | | | |
|--|------------------------|------------------|--------|-------------------|-----------|
| | Screening ¹ | Cycles 1, 2 | | Subsequent cycles | Off Study |
| | | Day 1 | Day 15 | Day 1 | |
| Informed Consent | X | | | | |
| History | X | X | X | X | |
| Concurrent meds | X | X | X | X | |
| Physical exam (Ht, Wt, BSA) | X | X | X | X | X |
| Vital Signs | X | X | X | X | |
| Performance Status | X | X | X | X | X |
| CBC with differential/ platelets | X | X | X | X | X |
| EKG | X | X | B | | |
| Urinalysis, urine protein & creatinine ² | X | X | | X | |
| Serum chemistry ³ | X | X | X | X | X |
| Fasting Lipid Panel | X | X | | X | X |
| Qualitative β -HCG ⁴ | X | X | | X | |
| Hepatitis B and C screen ⁵ | X | | | | |
| Pazopanib | | X-----X | | | |
| Everolimus | | X-----X | | | |
| Adverse event evaluation | | X-----X | | | X |
| Tumor measurements | X | | A | A | X |
| Radiologic evaluation | X | A | | | X |

1. Screening labs may be used as cycle 1 day 1 labs if performed within 7 days of initiation of study therapy.

2. If UPC ≥ 1 then a 24 hour urine protein must be assessed.

3: Albumin, alkaline phosphatase, total bilirubin, calcium, fasting glucose, LDH, phosphorus, total protein, SGOT [AST], SGPT [ALT], serum sodium, potassium, chloride, bicarbonate, BUN, magnesium, uric acid, amylase, lipase, thyroid stimulating hormone (day 1 of each cycle only).

Monitor serum liver tests before initiation of treatment with pazopanib and at weeks 3, 5, 7 and 9. Thereafter, monitor at Month 3 and Month 4, and as clinically indicated. Periodic monitoring should continue after Month 4.

4. Urine or serum pregnancy test (women of childbearing potential) at screening and day 1 of each cycle (+/- 3 days).

5. Screening for hepatitis B : Prior to registrations, patients will be tested for hepatitis B viral load and serologic markers, HBV-DNA, HBsAg, HBs Ab, and HBc Ab. Patients with risk factors for hepatitis C should be tested using quantitative RNA-PCR

A. Tumor measurements should occur in the cycle 2 week 3, and every 2 cycles thereafter. Confirmatory scans should also be obtained 4 weeks following initial documentation of an objective response. If scans have been performed within 30 days before coming off treatment, they do not need to be repeated. If scans cannot be obtained (patients coming off treatment to go to hospice or have died), please document in study file.

B. Pre-dose EKG obtained at baseline, cycle 1 days 1, 15, and cycle 2 day 1 only.

9.2 Expansion cohort

| Test/Procedure | Screening | | Treatment Cycles 1, 2 (28 day cycles) | | Subsequent cycles (28 day cycles) | Off Study | Survival |
|--|-------------|-------------|--|---------------------|--------------------------------------|---|----------|
| | -28 days | -14 days | Day 1 ¹ (±3 days) | Day 15 (±3 days) | Day 1 (±3 days) | 28 days after last dose (+/- 7 days) ⁹ | |
| Informed Consent | X | | | | | | |
| History | X | | X | X | X | X | |
| Concurrent Medications | X | | X | X | X | X | |
| Physical Exam | X | | X | X | X | X | |
| Vital Signs | | X | X | X | X | X | |
| Performance Status | X | | X | X | X | X | |
| CBC with Differential/ Platelets | | X | X | X | X | X | |
| Amylase and lipase | | X | X | | X | | |
| EKG | | X | X | | | | |
| Urinalysis, Urine Protein & Creatinine ² | | X | X | | X | X | |
| Serum Chemistry ³ | | X | X | X | X | X | |
| TSH | | X | X | | X | | |
| PT/INR, PTT | | X | | | | | |
| HbA1c ⁷ | | X | | | | | |
| Fasting Lipid Panel | | X | X | | X | X | |
| Qualitative β-HCG ⁴ | | X | X | | | | |
| Hepatitis B and C Screen ⁸ | | X | | | | | |
| Pazopanib | | | X-----X | | | | |
| Everolimus | | | X-----X | | | | |
| Adverse Event Evaluation | | | X-----X | | | | X |
| Radiologic Evaluation ^{5,6} | X | | | | X | X | |
| Survival Follow-Up | | | | | | | X |

1. Cycle 1 Day 1 evaluations are to be conducted within 1-week prior to start of protocol therapy. Screening labs may be used as Cycle 1 Day 1 labs if drawn within 7 days of initiating study therapy.

2. If UPC ≥ 1, then a 24 hour urine protein must be assessed.

3. Albumin, alkaline phosphatase, total bilirubin, calcium, fasting glucose, total protein, SGOT [AST], SGPT [ALT], serum sodium, potassium, chloride, bicarbonate, BUN, uric acid, magnesium, LDH, phosphorus

4. Urine pregnancy test (women of childbearing potential) at screening and cycle 1 day 1 only.

5. Radiological imaging should occur every 8 weeks, following cycle 1 day 1.

6. If scans have been performed within 30 days before coming off treatment, they do not need to be repeated as an off-study assessment. If scans cannot be obtained (e.g. patients coming off treatment to go to hospice or patients have died), please document in study file.

7. Applies to patients with uncontrolled diabetes mellitus

8. Screening for hepatitis: Prior to registrations, all patients will be tested for hepatitis B serologic markers (HBsAg, HBs Ab, and HBc Ab, HBV-DNA) and for hepatitis C (using quantitative RNA-PCR)

9. This visit can be foregone for patients who are too unwell to attend or for other reasons at the investigator's discretion. Patients may be contacted by phone to assess resolution of toxicities and may be contacted for survival follow up.

10. MEASUREMENT OF EFFECT

Objective response rate is the primary endpoint of the expansion cohort of this trial and participants will be assessed by RECIST v1.1 criteria. For the purposes of this study, participants should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of an objective response.

10.1 Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee v. 1.1⁵⁷. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. All participants who receive at least one dose of study treatment will be evaluable for response from the time of their first treatment. These participants will have their response classified according to the definitions stated below.

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥ 20 millimeters (mm) using conventional techniques (CT, MR1, x-ray) or ≥ 10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease,

abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum. If lymph nodes are to be included in the sum, then as noted above, only the short axis of the lymph node is added into the sum. The baseline sum will be used as the reference by which to characterize the objective tumor response.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted at each follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

10.1.4 Response Criteria

10.1.4.1 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 (or short axis for lymph nodes), taking as reference the baseline sum.

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

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

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

10.1.4.2 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 subject to be considered in complete clinical response

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

Progressive Disease (PD): Appearance of one or more new lesions (new lesions must be $>$ slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease status.

10.1.4.3 Evaluation of Best Overall Response

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

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Response for this Category Also Requires: |
|---|--------------------|-------------|------------------|--|
| CR | CR | No | CR | ≥4 wks confirmation |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks confirmation |
| PR | | | 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: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as " <i>symptomatic deterioration</i> ". Every effort should be made to document the objective progression even after discontinuation of treatment. | | | | |

10.1.5 Duration of Response

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

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

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

10.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or death, or is censored at the time of last disease evaluation.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at <http://ctep.cancer.gov/reporting/ctc.html>.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days (or 5 half-lives, whichever is longer) of the last dose of study medication. Participants who experience an ongoing adverse event or related to a study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.2.2 Serious adverse event (SAE)

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

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;

- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care and social reasons in the absence of any deterioration in the patient's general condition

11.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.2.3.2. Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.

- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

11.4 Reporting Adverse Events

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

All SAEs, regardless of “expectedness” or “causality” must be reported to the Principal Investigator (or Protocol Chair), Dr. Mark Pomerantz, via fax within 24 hours of learning of the event. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. All SAEs should be recorded on a MedWatch 3500a form. Please fax all supporting documentation as it becomes available.

The contact information for SAE reporting is as follows:

Mark Pomerantz, MD
Dana-Farber Cancer Institute
mark_pomerantz@dfci.harvard.edu

11.5 Novartis and GlaxoSmithKline Notification by Investigator

11.5.1 Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (see Section 11.2.2) that occur after the start of the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported as serious adverse events.

The participating investigator must report each serious adverse event, regardless attribution, to the Principal Investigator (or Protocol Chair) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation. The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E), and Glaxo-Smithkline. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form). **All events must be reported to both Novartis Pharmaceuticals DS&E Department [by FAX (877-778-9739)], and to GlaxoSmithkline [by e-mail to USNAPS@gsk.com and kamalnayan.h.bhatt@gsk.com OR fax to US-Case Management Group (fax 919-483-5404) and Kamal Bhatt (fax: 610-675-2632) within 24 hours of learning of the event's occurrence.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days. Any serious adverse event occurring after the patient has started the first dose of study treatment and until 30 days after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 30 days after study discontinuation need only be reported if a relationship to the GlaxoSmithkline or Novartis study drugs is suspected.

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

For Concomitant Medications, all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.5.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator (or Protocol Chair) on the toxicity Case Report Forms.

11.6 Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

In the event of a multi-center study, the Principal Investigator (or Protocol Chair) will report adverse events and serious adverse events from all participating sites to the DFCI IRB according to the IRB's policies and procedures in reporting adverse events.

11.7 Food and Drug Administration (FDA) Notification by Sponsor-Investigator

If this study is not IND-exempt, the Sponsor-Investigator will report to the FDA any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational

agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at <http://www.fda.gov/medwatch/getforms.htm>.

11.8 Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

| Form | Submission Timeline |
|------------------------------|--|
| Eligibility Checklist | Complete prior to registration with QACT |
| On Study Form | Within 14 days of registration |
| Baseline Assessment Form | Within 14 days of registration |
| Treatment Form | Within 10 days of the last day of the cycle |
| Adverse Event Report Form | Within 10 days of the last day of the cycle |
| Response Assessment Form | Within 10 days of the completion of the cycle required for response evaluation |
| Off Treatment/Off Study Form | Within 14 days of completing treatment or being taken off study for any reason |
| Follow up/Survival Form | Within 14 days of the protocol defined follow up visit date or call |

12.2 Safety Meetings

There will be monthly conference calls between the research team at the DF/HCC and the research team at Memorial Sloan-Kettering Cancer Center during the expansion phase of the trial to monitor safety and accrual. The attendee's for this will routinely include the principal investigators (or their designees), research coordinators, Research Nurses, and, as needed, investigational pharmacists. In addition, input during these teleconferences may be obtained from the clinical development teams both at Novartis and GlaxoSmithKline, as needed.

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other

necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. Increases in drug dose or duration of exposure of subjects,
2. Significant changes in the study design (e.g. addition or deletion of a control group),
3. Increases in the number of invasive procedures,
4. Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- Changes in the staff used to monitor trials
- Minor changes in the packaging or labeling of study drug.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6)
www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
 - Title 21 Part 11 – Electronic Records; Electronic Signatures
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
 - Title 21 Part 50 – Protection of Human Subjects
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
 - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
 - Title 21 Part 56 – Institutional Review Boards
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
 - Title 21 Part 312 – Investigational New Drug Application
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures
www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded

data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix D.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

This is a standard 3+3 design Phase I study with an expansion cohort at the recommended Phase II dose to further explore the activity and safety of the regimen.

14.1 Study Design/Endpoints

Phase I:

The primary endpoint is to determine the MTD and DLT's of the combination of everolimus and pazopanib. Safety and incidence of dose-limiting toxicities will be the primary outcome parameters. All patients in a dose cohort will complete 28 days (1 cycle) of combination treatment prior to the treatment of any patient at a higher dose level. If a patient does not complete the 28 days of treatment for reasons that are clearly not adverse events related to treatment, then that patient will be replaced, up to three per dose level. If more than three patients need to be replaced on a dose level, then the reasons will be re-evaluated before continuing. There will be no inpatient dose escalation. Pazopanib and everolimus will be escalated according to the standard 3+3 Phase I methodology and dose escalation rules (described in detail in Section 5.3.1). Once it is documented that the last patient in a cohort has completed 28 days of

therapy without evidence of excessive dose limiting toxicity, approval will be requested from the DF/HCC DSMB for dose escalation to the next dose level will occur. Successive cohorts of patients will be accrued to determine the maximum tolerated dose that results in <33% dose-limiting toxicities with the combination of everolimus and pazopanib in patients with metastatic kidney cancer. Up to six patients will be treated at the MTD before proceeding to the expansion cohort.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Toxicities will be summarized as number and percent of patients, separately by dose cohort. Other safety data (e.g. electrocardiogram, vital signs, special tests) will be considered as appropriate.

Adverse events will be summarized by presenting, for each dose cohort, the number and percentage of patients having any adverse event, having an adverse event in each body system, and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Descriptive statistics will be calculated to characterize the disease and previous treatment features as well as the details of protocol therapy. Toxicities will be tabulated by grade for each dose cohort and overall for all patients accrued to the Phase I study.

The probabilities of dose escalation for various true DLT rates are summarized below:

| | True Probability of DLT at Current Dose | | | | | | |
|------------------------------------|---|------|------|------|------|------|------|
| | 0.10 | 0.20 | 0.30 | 0.40 | 0.50 | 0.60 | 0.70 |
| Probability that dose is escalated | 0.91 | 0.71 | 0.49 | 0.31 | 0.17 | 0.08 | 0.03 |

Expansion cohort:

The primary objective is to evaluate the safety and efficacy of the combination of pazopanib and everolimus in previously treated advanced urothelial carcinoma patients. The proportion of patients achieving objective response (OR) defined as complete or partial response per RECIST criteria as their best overall response is the primary endpoint. Simon's two-stage design is employed to minimize accrual if treatment with pazopanib and everolimus is not effective. Achieving objective response in this population has historically been difficult. There no FDA approved second line therapy for urothelial cancer. The only European approved therapy in this setting is Vinflunine with a response rate of 9%.(48) The null hypothesis for this study is assumed to be 10%.

Twenty-nine patients will be enrolled. Only eligible patients who start protocol therapy will be included in the response analysis. The first stage will accrue n=20 patients (n=18 eligible treated patients). If 3 or more objective responses are observed among the first stage cohort then an additional 9 patients will be accrued (n=8 eligible treated patients). If 5 or more responses are observed in the 26 eligible patients who started protocol therapy

then the combination of pazopanib with everolimus will be considered promising. The operating characteristics of this design are summarized below. If the true OR rate is 10%, the probability of stopping early at the first stage is 0.734 and the probability of accepting treatment for further study is 0.099 (Type I error). If the true OR rate is 30%, the probability of concluding the treatment is promising is 0.904 (power). Upon completion of the study, the true response rate will be estimated and an exact 90% confidence interval constructed.

| | True Underlying Response Rate | | | | |
|---|-------------------------------|--|-------|-------|-------|
| | | | 20% | 25% | 30% |
| Probability of Stopping Early (<3/18) | | | 0.271 | 0.135 | 0.060 |
| Overall Probability of Concluding Effective ($\geq 5/29$) | | | 0.577 | 0.781 | 0.904 |

14.2 Sample Size/Accrual Rate

Phase I: 2 patients per month, with a maximum of 30 patients

Expansion cohort: 3 patients per month, with a maximum of 25 patients

14.3 Stratification Factors

N/A

14.4 Analysis of Secondary Endpoints

Phase I:

Pharmacokinetic parameters will be analyzed to determine whether pharmacologically significant drug interactions are present between everolimus and pazopanib. The concentration of everolimus in whole blood and plasma will be determined using a validated assay involving high performance liquid chromatography with electrospray ionization mass spectrometric detection. Time points will be determined as the difference between the midpoint of the blood collection interval and starting time of dose administration. Concentration-time profiles will be analyzed by noncompartmental methods and/or nonlinear least squares regression using Professional version 4.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and

variables will be calculated according to standard equations. Descriptive summaries of PK parameters (C_{trough}, T_{1/2} and C_{max}) will be provided by dose cohort.

Secondary

Secondary endpoints will evaluate safety, progression-free survival (PFS), overall survival (OS) and duration of response. Duration of response is calculated for objective responders and defined as the time in months from the first observation of a response (e.g., the first time that the appropriate RECIST 1.1 criteria was observed for confirmed responders) to the first documented progression or death due to any cause, whichever occurs first. Duration of response is censored at the date of last disease evaluation for patients who are known to be alive and who have not relapsed after a CR or PR. Progression-free survival is calculated as the months between registration and documented PD as determined by RECIST 1.1, or death due to any cause, whichever occurs first. Overall survival is defined as the time in months from registration to death due to any cause or, censored at the date last known alive. Patients alive without disease progression will be censored at the date of last disease evaluation. Time to event data will be estimated with the Kaplan-Meier method. Efficacy will further be described by 4- and 12-month PFS and OS rates along with 90% CIs. Descriptive statistics will be used to characterize the disease and previous treatment features as well as the details of protocol therapy.

Toxicity

All patients who receive treatment will be included in toxicity analyses. A summary of the incidence of all treatment-related grade 3-5 toxicities will be provided as maximum grade by toxicity type and body system. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Overall maximum grade 3 or higher treatment-related toxicity rates in all treated patients will be calculated. The table below shows the 90% confidence intervals for 0, 2, 4, and 6 patients with grade 3 or higher toxicity in a total of 29 treated patients.

| Observed Number of Patients with Grade ≥ 3 Toxicity | Grade ≥ 3 Toxicity Rate | 90% Confidence Interval for True but Unknown Grade ≥ 3 Toxicity Rate |
|--|------------------------------|---|
| 0 | 0.0% | (0.0%, 9.8%) |
| 2 | 6.9% | (1.3%, 20.2%) |
| 4 | 13.8% | (4.9%, 28.9%) |
| 6 | 20.7% | (9.4%, 36.8%) |

Exploratory

Relevant somatic and germline alterations will be identified by adaptation and modification of discovery-oriented algorithms in common use at the Broad Institute and MSKCC. We will also apply a series of computational algorithms that predict neutral, detrimental or activating variants. Upon completion, we will deliver a list of somatic and germline variants that perturb cancer genes and associated cellular pathways, associated with response to therapy in this cohort. Relevant associations between mutation status and treatment outcome will be assessed on an exploratory basis, and relevant targeted sequencing may be performed in non-responders to further understand the association between response to study therapy and somatic alterations.

14.5 Reporting and Exclusions

14.5.1 Evaluation of toxicity. Any participant who has received at least one dose of study therapy will be evaluable for toxicity. Patients who experience toxicity not meeting the definition of DLT but do not complete 28 days of study treatment will be replaced. Reasons for not completing 28 days of therapy will be reviewed.

14.5.2 Evaluation of response. All participants who received treatment will be assessed for response to treatment, even if there are major protocol treatment deviations. Patients who did not receive any dose of study medication will not be included in the analysis. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, and unknown (not evaluable, insufficient data).

All conclusions should be based on all eligible and treated participants who received protocol therapy. Subanalyses will then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified. However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis will be clearly reported. The 95% confidence intervals will be provided.

Pregnancy

Preclinical data regarding reproductive toxicity is described in the most recent Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth

defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

15. PUBLICATION PLAN

The phase I results of this study will be submitted for presentation as an abstract in 2012. Full results will plan on being published in a peer reviewed publication in 2013. The expansion cohort results will be submitted for abstract presentation in 2014 and submitted for publication in 2015.

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17. APPENDICES Appendix A

Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|-------------------------------|---|-----------------------------|--|
| Grade | Description | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 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). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active 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. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

Appendix B

Pazopanib Blood Pharmacokinetic Collection and Handling

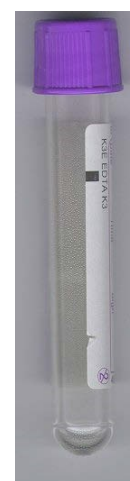
Pharmacokinetic Sample Supplies

GlaxoSmithKline will provide all tubes for blood collection, storage, and labels with the visit name and time of sample collection (tubes sent as bulk shipment with separate labels).

Blood samples for the determination of plasma pazopanib concentrations will be collected into 2mLEDTA vacutainers. The blood samples will be collected into tubes and immediately placed on ice. Samples will be centrifuged at 3000 RPM for 10 minutes under chilled conditions (approximately 4°C). Transfer *no more than* 750µL of the resultant plasma into appropriately labelled 1.4mL Matrix TrakMate polypropylene tubes and stored frozen (within 60 minutes of the sampling time) at -20°C.

PK Blood Collection Tubes Labels

Please place labels on the tubes vertically, as they are found in the picture. Do not place them horizontally around the tube, resulting in a tag.



DMPK Shipping Guide- Pazopanib

Specific regulations exist for the shipment of biological specimens. The Department of Drug Metabolism and Pharmacokinetics (DMPK) requires the use of IATA/ICAO regulations when specimens are shipped on our behalf.

It is the sender's responsibility to abide by all regulations.

Notification of Shipment

Please remember to notify the department of DMPK **as soon as possible, but at least two days** in advance of any shipment. **DO NOT** leave a message on an answering machine. Please state protocol number, expected shipping date, carrier, estimated time of arrival and airway bill number if applicable.

Frozen samples should be shipped on solid carbon dioxide.

Shipping Days

Please ship **MONDAY through WEDNESDAY** only

Please ensure that wherever possible samples are transported so as to arrive between the hours of 09:00 and 16:00.

UM Sample Management Contact Details:

The shipping boxes must be clearly labeled with the following address:

GlaxoSmithKline

Department of Drug Metabolism and Pharmacokinetics

Mail Stop UW2710

709 Swedeland Road

King of Prussia, PA 19406

USA

Attn: Kathleen Dolce/ Josh Albert

| | Phone # | Mail Code | FAX |
|----------------|--------------|-----------|--------------|
| Kathleen Dolce | 610-270-6757 | UW2710 | 610-270-4971 |
| Josh Albert | 610-270-6549 | UW2710 | 610-270-4971 |
| Michael Adamek | 610-270-4658 | UW2710 | 610-270-4971 |

Packaging instructions:

NOTE: Do not let samples thaw while packaging!

1. Place individual tubes into Matrix 96 well rack. Place rack into a large bag with absorbent material. Place bags with racks in bottom of cooler.
2. Fill box completely with dry ice and put top on cooler.
3. Enclose a copy of the requisition forms, corresponding to the samples in that box, in a bag or envelope and place on the top of the cooler.
4. Close the flaps and tape shut.
5. Complete the airbill and shipping labels, according to the directions below. Affix airbill to top of shipping box.

Example UPS Airbill

UPS Next Day Air[®]
UPS Worldwide Express[™]
Shipping Document

See instructions on back. Visit UPS.com or call 1-800-PICK-UPS[®] (800-742-5877) for additional information and UPS Tariff/Terms and Conditions.

TRACKING NUMBER J208 320 056 6

1 SHIPMENT FROM

SHIPPER'S UPS ACCOUNT NO. _____

REFERENCE NUMBER **Protocol##Cost Center**

NAME _____ TELEPHONE _____

COMPANY _____

STREET ADDRESS _____

CITY AND STATE _____ ZIP CODE _____

2 EXTREMELY URGENT DELIVERY TO

NAME **Kathy Dolce- UW2710** TELEPHONE **610-270-6757**

COMPANY **GlaxoSmithKline**

STREET ADDRESS **709 Swedeland Road** DEPT./FLR. _____ Residential Delivery ☐

CITY AND STATE **King of Prussia PA** ZIP CODE **19406**

3 WEIGHT _____ **4 SHIPPER RELEASE** ☐

5 TYPE OF SERVICE ☒ **NEXT DAY AIR** ☐ **EXPRESS (INTL)**

6 OPTIONAL SERVICES ☐ **SATURDAY PICKUP** ☐ **SATURDAY DELIVERY**

7 ADDITIONAL HANDLING CHARGE ☐ An Additional Handling Charge applies for certain items. See instructions.

8 METHOD OF PAYMENT ☐ **BILL SHIPPER'S ACCOUNT** ☒ **BILL RECEIVER** ☐ **BILL THIRD PARTY** ☐ **CREDIT CARD** ☐ **AMERICAN EXPRESS** ☐ **DISCOVER** ☐ **MASTERCARD** ☐ **VISA** ☐ **CHECK** ☐

9 RECEIVER'S/THIRD PARTY'S UPS ACCT. NO. OR MAJOR CREDIT CARD NO. **301923** **EXPIRATION DATE** _____

10 SHIPPER'S SIGNATURE **X**

DATE OF SHIPMENT _____

UPS COPY

***Please use one airbill per box**

You must enter on the airbill:

- Your site's address

- The weight of the package in lbs.
- The weight of the dry ice in KG
- Sender's signature

Shipping Box

1. Complete the following label found on the specimen shipping box:
 - Address/return address label (fill in blanks)
 - Carbon dioxide, solid [Dry Ice] UN1845 #KG (fill in blank). **Note: This weight should match the weight on the airbill.**
2. Prior to shipping, notify the following individuals of the airbill number(s), the number of boxes shipped, the nature of the shipment (i.e.: medical specimens), and scheduled shipment/pick-up and arrival date.
 - UPS Office at 1-800-877-1497 and give them account# **301923**.
 - GlaxoSmithKline DMPK via the FAX page located in the PK Sample Information and Shipping Notebook (Fax: 610-270-4971).

Cycle 1 shipping Form – Include with Pazopanib PK samples

STUDY NUMBER

Pazopanib Plasma Requisition Form

A copy of this completed page must accompany the samples being shipped to GlaxoSmithKline. Please keep a copy for your records. Please use a new sheet for each subject/shipment.

Subject Number: _____

Cycle 1

| Day | Time-point | Time | ✓ if included in this shipment | Comments | Rec'd By |
|-----|------------|------|--------------------------------|-----------------|----------|
| 1 | 0h | | | | |
| 1 | 1h | | | | |
| 1 | 2h | | | | |
| 1 | 4h | | | | |
| 1 | 6h | | | | |
| 1 | 24h | | | | |
| 1 | 48h | | | (If Applicable) | |
| 15 | 0h | | | | |
| 15 | 1h | | | | |
| 15 | 2h | | | | |
| 15 | 4h | | | | |
| 15 | 6h | | | | |
| 15 | 24h | | | | |
| 15 | 48h | | | (If Applicable) | |

Cycle 2 Shipping Form – Include with Pazopanib PK samples

STUDY NUMBER
Pazopanib Plasma Requisition Form

A copy of this completed page must accompany the samples being shipped to GlaxoSmithKline. Please keep a copy for your records. Please use a new sheet for each subject/shipment.

Subject Number: _____

Cycle 2, 4

| Cycle | Day | Time-point | Time | ✓ if included in this shipment | Comments | Rec'd By |
|-------|-----|------------|------|--------------------------------|----------|----------|
| 2 | 1 | 0h | | | | |
| 4 | 1 | 0h | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Sample Collection and Storage for Pazopanib

At each of the sampling times, blood samples (2 mL) will be drawn into a K3 EDTA vacutainer, and centrifuged for 10 minutes to separate the plasma. The plasma will be transferred into pre-labeled storage tubes for analysis of paclitaxel and stored at approximately -20°C. Sample handling from collection to storage should not exceed 60 minutes. A blood sample will be taken prior to the pazopanib dose, and at 0, 1, 2, 4, 6, and 24 hours. If patients are treated on dose level -1, there will be a 48 hour blood draw (pre-dose) as well.

All tubes must be frozen in an upright position to keep the plasma in the bottom of the tube. Until assayed, the samples must remain frozen in a freezer set at approximately -20°C or when shipping in a box with dry ice. Prior to collection, the collection tube and plasma storage tube must be labeled with the corresponding bar-coded labels provided by GSK. The sample labels will include Protocol Number, Analyte, Subject Number, Relative Sample Time, Cycle and Dosing Day. The labels must be placed along the length of the tube so the bar code can be easily read. Tape must not be used to secure the labels otherwise the tube will not fit into the autoanalyzer test tube rack. The labels are high quality and will not peel off of the tube even under extreme conditions.

The sample will be centrifuged at approximately 1000 x g for 10 to 15 minutes. The resulting plasma will be transferred to the corresponding pre-labeled polypropylene storage tube (2mL). See shipping instructions with regard to packing the samples, enclosing a manifold with a sample inventory, and notification of the analytical sites prior to shipping.

APPENDIX C

Instructions for Collecting, Processing, Storing, and Shipping Everolimus Pharmacokinetic Sample

C.1 Venous access

Pharmacokinetic samples may be collected from a central catheter for this study because everolimus is given orally.

For patients without a central catheter, place a large gauge peripheral catheter (e.g., 19 or 20 gauge angiocath straight set with T-connector, or similar IV access device) in an arm vein for the collection of pharmacokinetic blood samples on days when multiple samples are to be collected. Maintain patency of the catheter between blood draws using either a heparin lock (e.g., 10 U/mL in normal saline) or a slow drip of Normal Saline for Injection, USP (e.g., 10 mL/hr).

Blood may be obtained directly by venipuncture on days when only a single pharmacokinetic blood specimen is scheduled for collection.

When sampling through a catheter, begin to clear the catheter approximately 1 min before the specified sample time by withdrawing the lock solution and approximately 0.5 mL of blood into a syringe. Remove and properly dispose the syringe used to clear the catheter. The catheter should be well-flushed after collecting each sample.

C.2 Timing

A battery-powered digital timer/stopwatch programmed to operate continuously as a 24-hr clock will be used to accurately monitor drug administration and sample collection times. The same timer must be allowed to run without interruption until the last blood specimen has been obtained from the subject during the first cycle of therapy.

Timer readings will be noted at the precise time that the infusion is started and ended, as well as at the beginning and ending times of the blood sample collection intervals.

Readings of the digital timer must be directly recorded on a copy of the appropriate DF/HCC Pharmacokinetic Dosing and Blood Collection Time Form' (see below).

C.3 Sample collection

As indicated in section 8.1, two blood samples are to be collected in 2.0 mL Vacutainer plastic whole blood collection tube with spray-coated K₂-EDTA (Becton-Dickinson, item no. 367863) at each and every time point.

C.4 Sample processing and storage

Promptly mix the blood collection tubes by gently inverting 6-times.

Transfer the whole blood from one tube collected at each time point directly into a 4.5 mL self-standing polypropylene microcentrifuge cryogenic tube with external threads (Fisher Scientific, cat. no. 12-565-291).

Centrifuge the other tube of blood collected at each time point at 1,300 x g for 10 min within 15 min after collection. Separate the plasma from the blood cells using a pipette and transfer the plasma it into a polypropylene cryogenic storage vial with external threads.

Affix a pre-printed labels (protocol number, patient entry no., sample no., scheduled sample time) to the cryotube, oriented lengthwise toward the upper part of the tube. Do not place the label over the vial cap. Hand-written information on sample tube labels is absolutely prohibited.

Completely cover the label with protective cryogenic freezer tape (e.g., Fisher Scientific, cat. no. 11-867B).

Place the tube on crushed dry-ice until stored in a freezer maintained at $\leq -70^{\circ}\text{C}$ until packaged for shipment.

C.5 Time forms and sample tube/vial labels

Computer files for dose administration and sample collection time forms and specimen tube labels will be placed in a subdirectory located on a secure network server (W:\PHASE1RD) maintained by Partners HealthCare System (PHS) Information Resources. All members of the clinical, laboratory, and administrative staff involved with Phase I studies should have read-only access to this subdirectory, which may be obtained by contacting Susan Oliveira by email (see PHS Global e-mail directory).

The files are placed under the following subdirectories: PK_Time_Forms; PK_Tube_Labels.

Files for the PK time forms are to be printed directly from the file stored on the network server for each subject study. Since changes may be periodically made to these forms, they should not be copied onto user personal computers and staff members are instructed not to make photocopies of blank forms.

The PK_Tube_Label files are templates that are intended to be copied and edited by replacing the word 'code' with the patient entry number using the MS Word edit/replace all function and printed on an Avery 5260 label sheet. Hand-written information on sample tube labels is absolutely prohibited. There are separate sets of labels for blood collection tubes and sample storage tubes. Blood collection tubes should be pre-labeled.

C.6 Sample shipment

Contact Susan Oliveira (tel: 617-726-5868 or 617-726-5854; e-mail: soliveira2@partners.org) or Dr. Jeffrey Supko (email: supko.jeffrey@mgh.harvard.edu) to arrange transportation of each complete set of samples to the DF/HCC Cancer Pharmacology Core at the Massachusetts General Hospital, 55 Fruit Street, Room GRJ1025, Boston, MA 02114.

APPENDIX D

Drug Supply Request Form

PI:

GSK Study Number:

Title of Study:

In order to facilitate your shipment for drug supply, please fill in the following information. If you have any questions regarding completing this form, please contact Kamal Bhatt, via telephone at (610)917-5768 or via email at Kamalnayan.H.Bhatt@gsk.com.

The full shipping address for drug supply:

Institution Name

Full Street Address (with contact name/phone #)

Specific dosage requested

Amount Requested

For CRT (investigator initiated) studies, the PI holds the IND and is therefore responsible for following CFR and GCP for labeling and dispensing (21 CFR 312.6). GSK will ship labeled pazopanib bottles in a sealed carton (68 tabs per bottle for pazopanib 400mg and 34 tabs/btl for pazopanib 200mg). A label will be affixed to each carton identifying the product, strength and number of bottles. In addition, a packing slip will be enclosed with the drug name, strength, lot/batch #, storage conditions, and expiration/retest date.

Appendix E: Genes in NGS sequencing assay

| | | | | | | | | | | | | | |
|----------|----------|--------|----------|---------|--------|----------|--------|--------|--------|---------|--------|----------|-------|
| ABL1 | BCL6 | CDK8 | DNMT3A | ERBB3 | FLT3 | HRAS | KDM6A | MET | NFKB1 | PHOX2B | PTPN11 | SMARCA4 | TOP1 |
| ABL2 | BCOR | CDKN1A | DNMT3B | ERBB4 | FLT4 | HSP90AA1 | KDR | MITF | NFKB2 | PIK3C2G | PTPRD | SMARCB1 | TP53 |
| AKT1 | BIRC2 | CDKN2A | E2F3 | ERG | FOXL2 | IDH1 | KEAP1 | MLH1 | NKX2-1 | PIK3CA | PTPRS | SMO | TP63 |
| AKT2 | BRAF | CDKN2B | EGFR | ESR1 | FUBP1 | IDH2 | KIT | MLL | NOTCH1 | PIK3CB | PTPRT | SOCS1 | TSC1 |
| AKT3 | BRCA1 | CDKN2C | EIF4EBP1 | ETV1 | GATA1 | IGF1R | KLF6 | MLL2 | NOTCH2 | PIK3CD | RAF1 | SOX2 | TSC2 |
| ALK | BRCA2 | CEBPA | EP300 | ETV6 | GATA2 | IGFBP7 | KRAS | MLL3 | NOTCH3 | PIK3CG | RARA | SPOP | TSHR |
| ALOX12B | BUB1B | CHEK1 | EPHA10 | EZH2 | GATA3 | IKBKE | LDHA | MLST8 | NOTCH4 | PIK3R1 | RB1 | SRC | U2AF1 |
| APC | CARD11 | CHEK2 | EPHA2 | FAM123B | GLI1 | IKZF1 | LGR6 | MPL | NPM1 | PIK3R2 | REL | SRSF2 | VHL |
| AR | CBL | CIC | EPHA3 | FAM46C | GLI3 | IL7R | LMO1 | MSH2 | NRAS | PIK3R3 | RET | STAG2 | WAS |
| ARAF | CBLB | CREBBP | EPHA4 | FAS | GNA11 | INPP4A | MAGI2 | MSH6 | NTRK1 | PKM2 | RICTOR | STK11 | WNK1 |
| ARHGAP26 | CCND1 | CRKL | EPHA5 | FAT1 | GNAQ | INPP4B | MAP2K1 | MTOR | NTRK2 | PLK2 | RNF43 | SUFU | WT1 |
| ARID1A | CCNE1 | CRLF2 | EPHA6 | FBXO11 | GNAS | INSR | MAP2K2 | MYB | NTRK3 | PNRC1 | ROR2 | TBK1 | XPO1 |
| ARID2 | CD79B | CSF1R | EPHA7 | FBXW7 | GOLPH3 | IRS1 | MAP2K4 | MYC | PAK7 | PPP2R1A | ROS1 | TEK | YAP1 |
| ASXL1 | CDC42EP2 | CTNNB1 | EPHA8 | FGFR1 | GRIN2A | IRS2 | MAP3K8 | MYCL1 | PALB2 | PRDM1 | RPTOR | TERT | YES1 |
| ATM | CDC73 | CYLD | EPHB1 | FGFR2 | GRM3 | JAK1 | MCL1 | MYCN | PARK2 | PREX2 | RUNX1 | TET1 | ZRSR2 |
| ATRX | CDH1 | DAXX | EPHB2 | FGFR3 | GSK3B | JAK2 | MDM2 | MYD88 | PARP1 | PRKAA2 | SDHB | TET2 | |
| AURKA | CDH11 | DDR2 | EPHB3 | FGFR4 | HDAC2 | JAK3 | MDM4 | NCOA2 | PAX5 | PRKAR1A | SETD2 | TGFBR2 | |
| BAP1 | CDK12 | DICER1 | EPHB4 | FH | HIF1A | JUN | MED12 | NF1 | PBRM1 | PRKCI | SF3B1 | TMPRSS2 | |
| BCL2L1 | CDK4 | DIS3 | EPHB6 | FLCN | HMGA2 | KCNJ5 | MEF2B | NF2 | PDGFRA | PTCH1 | SHQ1 | TNFAIP3 | |
| BCL2L11 | CDK6 | DNMT1 | ERBB2 | FLT1 | HNF1A | KDM5C | MEN1 | NFE2L2 | PDGFRB | PTEN | SMAD4 | TNFRSF14 | |