CTEP Protocol #8880
Clinical Center Protocol # 12-C-0009

TITLE: Phase Ib Study of the Combination of Pazopanib, an Oral VEGFR Inhibitor, and ARQ 197 (Tivantinib), an Oral MET Inhibitor, in Patients With Refractory Advanced Solid Tumors

Abbreviated Title: Phase I of Pazopanib and ARQ 197 in Solid Tumors

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NCI Supplied Agents: Pazopanib (NSC 737754)
ARQ 197 (NSC 750832)

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Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- Vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) signal transduction pathways have synergistic effects on promoting angiogenesis and growth factor expression. Hypoxia caused by treatment with VEGF inhibitors results in the upregulation of c-MET, the receptor for HGF. In a mouse model, combined blockade of VEGFR and c-Met significantly prolonged survival compared with inhibition of either target alone.
- We hypothesize that co-administration of the MET inhibitor ARQ 197 will prevent the adaptive response to hypoxia resulting from treatment with the VEGFR inhibitor pazopanib, and conversely, that co-administration of pazopanib will prevent the effect of increased VEGF and reduced thrombospondin 1 in tumors after treatment with ARQ 197. Therefore, the combination of these agents may result in improved antitumor effects.

Objectives:

- Establish the safety and tolerability of the combination of pazopanib with ARQ 197 in patients with refractory advanced solid tumors.
- Establish the maximum tolerated dose (MTD) of the combination of pazopanib with ARQ 197 in patients with refractory advanced solid tumors.
- Evaluate changes in MET and phospho-MET following treatment with pazopanib and ARQ 197 in patients with refractory advanced solid tumors.
- Determine the pharmacokinetics (PK) of pazopanib and ARQ 197.
- Determine and compare levels of total MET, phospho MET, HIF-1α, and epithelial-mesenchymal transition markers (e-cadherin, beta catenin) in tumor biopsy samples prior to and following administration of the study drugs.
- Determine and compare levels of circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of the study drugs.
- Determine polymorphisms in the CYP2C19 and correlate these with the observed toxicities, and the PK of ARQ 197.
- Evaluate antitumor activity of the combination of pazopanib and ARQ 197 in patients with refractory advanced solid tumors.

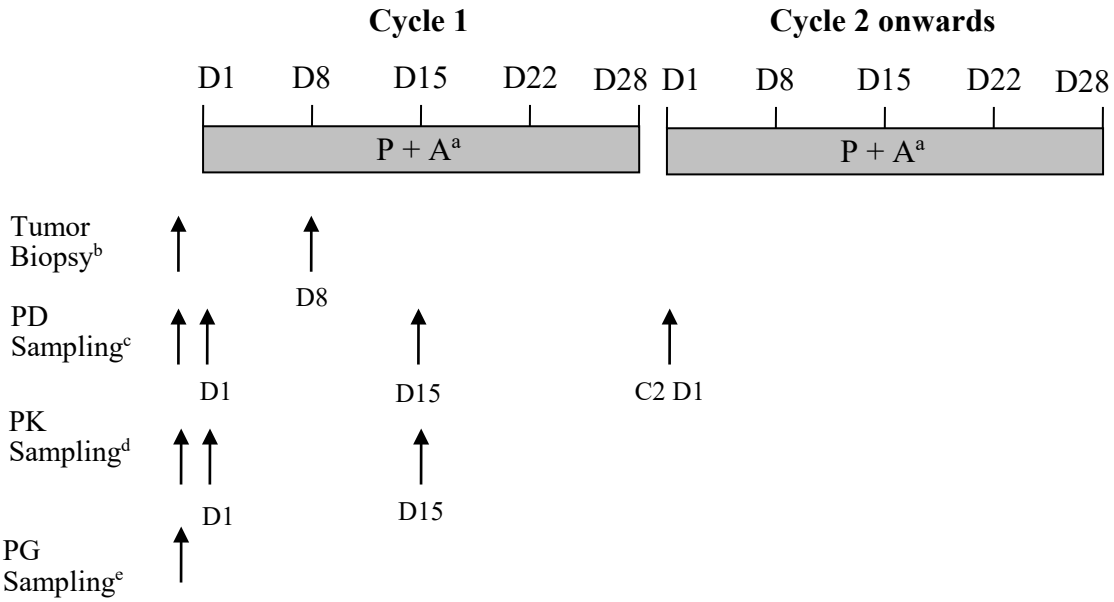
Eligibility:

- Adults with advanced, refractory solid tumors. Patients enrolling in the expansion cohorts must have advanced sarcoma, gastric cancer, and MET-expressing malignancies, have disease amenable to biopsy, and be willing to undergo pre-and post-treatment biopsies.

Study Design:

- ARQ 197 will be administered orally twice daily and pazopanib orally once daily, in 28-day cycles.
- Dose escalation will proceed using the traditional 3+3 design.
- Once the MTD is established, an additional cohort will be accrued for pharmacodynamic (PD) studies in tumor biopsies (required in the expansion phase). For the first week, patients will receive pazopanib alone to compare PK and PD results; combination therapy will be given from week 2 onwards.

SCHEMA: DOSE ESCALATION PHASE



[a] Pazopanib (P) po q day and ARQ 197 (A) po bid continuously throughout in patients on the dose escalation phase. Pazopanib will be taken on an empty stomach 1 hour before a meal and ARQ 197 will be taken with food.

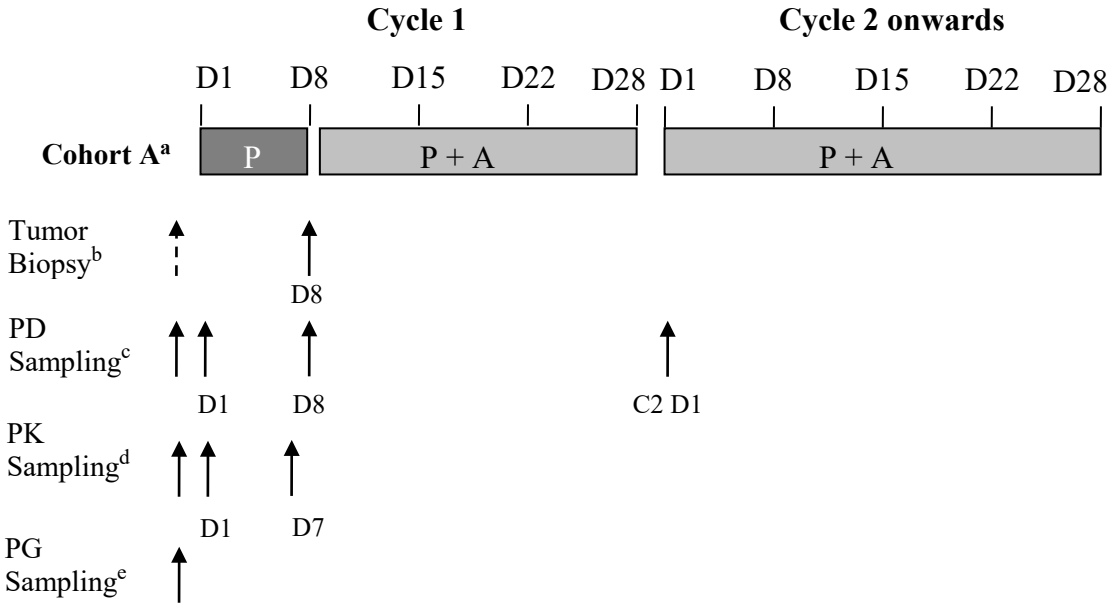
[b] Tumor biopsies (optional during the dose escalation phase) will be performed at baseline (pre-treatment) and on C1D8, 8-12 hours after the Day 7 evening dose of ARQ 197 (taken 1 hour after pazopanib).

[c] Blood samples for PD analyses collected at baseline (pre-treatment), on C1D1 (2, 4, and 6 hours after pazopanib), on C1D15 (pre-study drug administration), and on C2D1 (pre-study drug administration).

[d] Blood samples for PK analyses will be collected on C1D1, before drug administration and 1, 2, 4, 6, and 12 hours after administration of pazopanib (12-hour time point is pre-second dose of ARQ 197), and on C1D15 before drug administration and 1, 2, 4, and 6 hours after administration of pazopanib.

[e] A blood sample for pharmacogenomic (PG) analyses will be collected prior to drug administration on C1D1.

SCHEMA: EXPANSION PHASE



[a] Pazopanib (P) po q day taken on an empty stomach 1 hour before a meal and ARQ 197 (A) po bid taken with food.
Cohort A: Single-agent pazopanib from C1D1 to D7, then the combination of ARQ 197 and pazopanib from C1D8.

[b] Tumor biopsies (mandatory during the expansion phase) for **Cohort A** at baseline (pretreatment) **and** on C1D8 after pazopanib but before the first dose of ARQ 197.

[c] Blood samples for PD analyses collected at baseline (pre-treatment), on C1D1 (2, 4, and 6 hours after pazopanib), on C1D8 (pre-study drug administration), and on C2D1 (pre-study drug administration).

[d] Blood samples for PK analyses will be collected prior to drug administration and at multiple time points after drug administration in cycle 1 only:
Cohort A: D1, pre-dose and 1, 2, 4, 6, and 12 hours after administration of pazopanib; D7, pre-dose and 1, 2, 4, and 6 hours after administration of pazopanib.

[e] A blood sample for pharmacogenomic (PG) analyses will be collected prior to drug administration on C1D1.

Dose Escalation:

Dose Level	Pazopanib po q day	ARQ 197 po
-2	200 mg	120 mg QD
-1	400 mg	120 mg QD
1 (starting dose)	400 mg	120 mg BID
2	600 mg	120 mg BID
3	600 mg	240 mg BID
4	800 mg	240 mg BID
5	800 mg	360 mg BID
6*	600 mg	360 mg BID

*If dose level 5 is above the MTD, dose level 6 will be evaluated.

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1 OBJECTIVES

1.1 Primary Objectives

- Establish the safety and tolerability of the combination of pazopanib with ARQ 197 in patients with refractory advanced solid tumors.
- Establish the maximum tolerated dose (MTD) of the combination of pazopanib with ARQ 197 in patients with refractory advanced solid tumors.
- Evaluate changes in MET and phospho-MET following treatment with pazopanib and ARQ 197 in patients with refractory advanced solid tumors.

1.2 Secondary Objectives

- Determine the pharmacokinetics (PK) of pazopanib and ARQ 197.
- Determine and compare levels of total MET, phospho MET, HIF-1α, and epithelial-mesenchymal transition markers (e-cadherin, beta catenin) in tumor biopsy samples prior to and following administration of the study drugs.
- Determine and compare levels of circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) prior to and following administration of the study drugs.
- Determine polymorphisms in the CYP2C19 and correlate these with the observed toxicities, and the PK of ARQ 197.
- Evaluate antitumor activity of the combination of pazopanib and ARQ 197 in patients with refractory advanced solid tumors.

2 BACKGROUND

2.1 Targeting the VEGF and HGF Pathways

Activation of the independent vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) signal transduction pathways has synergistic effects on promoting the formation of new blood vessels and inducing the expression of a number of growth factors, chemokines, and cytokines, including c-MET, the tyrosine kinase receptor for HGF [1-3]. The mechanism for this synergistic interaction is not known, but overexpression of HGF and c-MET are associated with aggressive tumors and poor prognosis in several cancers [4-6]. Combination therapy with inhibitors of HGF and VEGF signaling might therefore have superior anti-angiogenic activity in patients with cancer than either agent alone [7].

Sennino and colleagues investigated whether inhibiting VEGF and c-MET had an effect on tumor growth and survival in a mouse model using XL184 (BMS-907351), a tyrosine kinase inhibitor that blocks VEGFR and c-MET, and an antibody selective for mouse VEGF [8]. This study also evaluated whether treatment with a VEGF inhibitor upregulates the expression of c-MET, as no in vitro data indicates that treatment with VEGF inhibitors results in both antitumor

activity and promotion of metastasis [9-11]. It has been suggested that one response to the hypoxia caused by treatment with VEGF inhibitors is upregulation of c-MET [12].

As shown in Figure 1, combination blockade of VEGFR and c-MET with XL184 significantly ($P < 0.05$) prolongs survival compared to treatment with vehicle or anti-VEGFR antibody alone in the RIP-Tag2 transgenic mouse model, a spontaneous and highly vascularized pancreatic islet cell cancer [8].

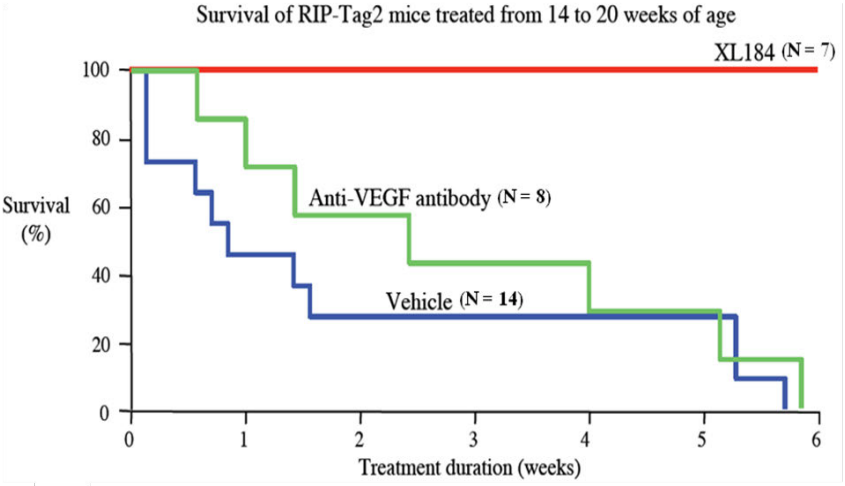

Figure 1: Increased survival of RIP-Tag2 transgenic mice following treatment with the VEGFR and c-MET inhibitor XL184 compared to treatment with anti-VEGF antibody or vehicle.

The extent of liver metastasis was also less in RIP-Tag2 mice treated with combination blockade of VEGFR and c-MET than in mice treated with anti-VEGF antibody alone (Figure 2).

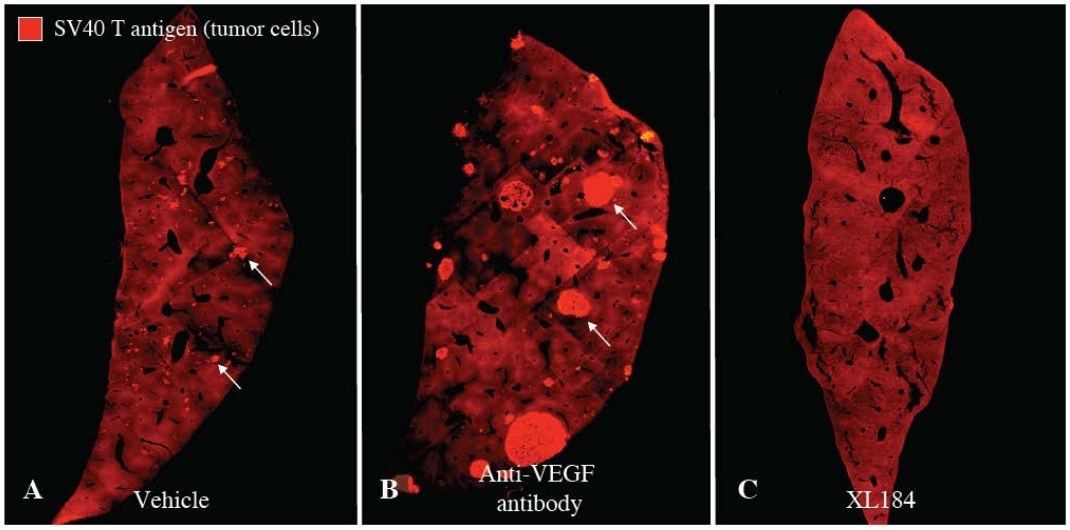

Figure 2: Confocal micrographs of liver sections stained for SV40 T-antigen (expression is limited to islet insulin-producing β cells) from RIP-Tag2 mice treated from 14 to 17 weeks of age with vehicle **(A)**, anti-VEGF antibody **(B)** or XL184 **(C)**. The number and size of liver metastases (indicated with white arrows) are greatest after treatment with anti-VEGF antibody, less prevalent (i.e., smaller and scattered) after treatment with vehicle, and undetectable after treatment with XL184 ($P < 0.05$, measured mm^2).

Of relevance to this protocol is that c-MET expression was significantly increased in pancreatic islet cell tumors in RIP-Tag2 mice after treatment with anti-VEGF antibody (Figure 3) [8]. Overexpression of c-MET is sufficient to induce hepatocellular carcinomas in transgenic mice [13, 14]. Data from the Vande Woude lab also support a role for HGF in promoting angiogenesis through upregulated expression of VEGF and downregulated expression of thrombospondin 1 (TSP-1), a key negative regulator of angiogenesis [4]. Agents that inhibit c-MET and VEGF are therefore of great clinical interest [7, 13, 15, 16].

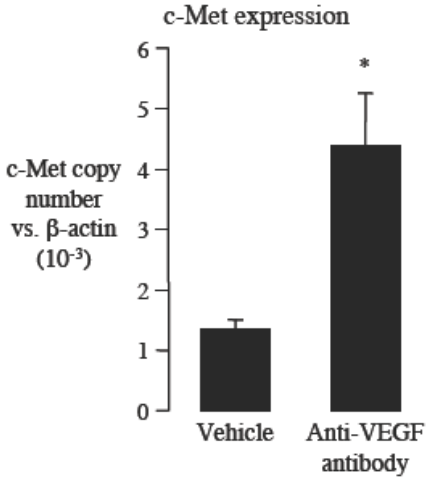

Figure 3: PCR measurements of c-MET expression in pancreatic islet cell tumors in transgenic RIP-Tag2 mice after treatment with vehicle or anti-VEGF antibody for 1 week. N = 5 mice/group. *P < 0.05 vs. vehicle.

2.2 Pazopanib

Pazopanib is a highly selective and potent inhibitor of VEGFR-1, -2 and -3, PDGFR-alpha, PDGFR-beta, and c-kit tyrosine kinases which are integral components of several cell signaling pathways aberrantly activated during carcinogenesis (Figure 4) [17-19]. Pazopanib has been shown to selectively inhibit VEGF-induced endothelial cell proliferation, angiogenesis and tumor growth in multiple human tumor xenograft models, including prostate, colon, lung, melanoma, breast, and renal cancer. Preclinical PK/PD studies have shown that a plasma concentration of ≥40 μmol/L pazopanib is required for optimal inhibition of VEGFR-2 in vivo [17].

Clinically, pazopanib has demonstrated activity in patients with renal cell cancer; current Phase I, II, and III trials of pazopanib as single therapy and in combination with paclitaxel or the tyrosine kinase inhibitor of HER2 and EGFR, lapatinib, are ongoing or planned. These trials are accruing patients with several tumor types including liver cancer, metastatic renal cell carcinoma, malignant glioma, non-small cell lung cancer, advanced breast cancer, multiple myeloma, ovarian cancer, and various types of sarcomas.

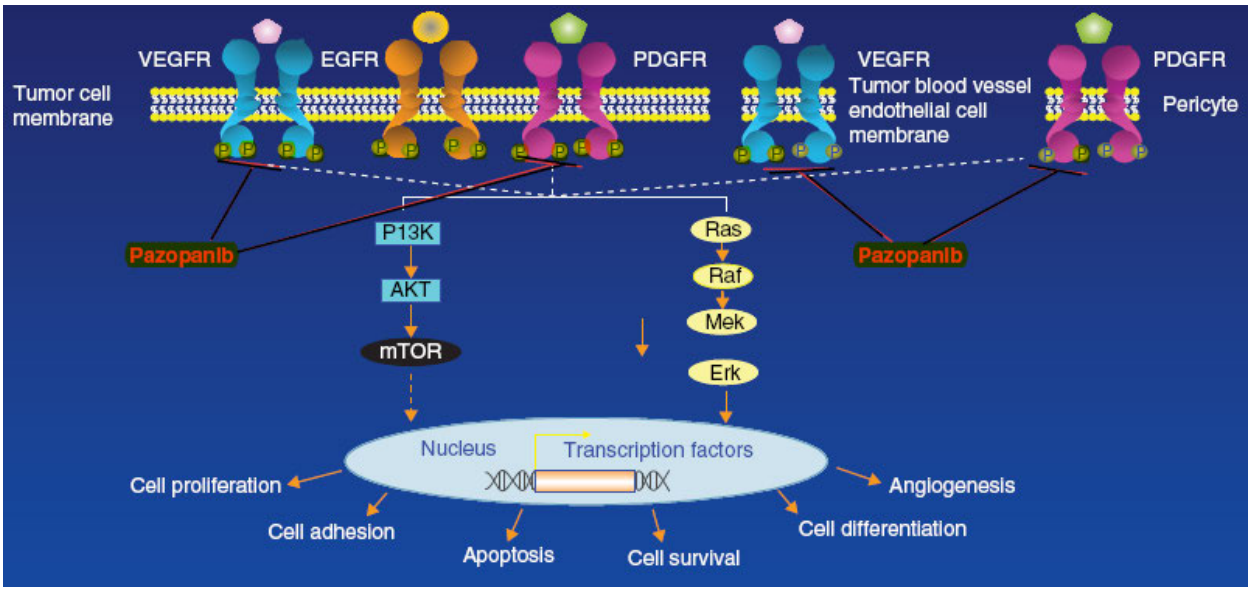

Figure 4: Outline of Pazopanib targets in multiple signaling pathways involved in tumor angiogenesis, proliferation, and survival [18].

Clinical Experience

Approximately 3000 subjects with cancer have been enrolled in clinical studies of pazopanib as of September 2009. In October 2009, the FDA approved pazopanib tablets for the treatment of subjects with advanced renal cell carcinoma (RCC). In addition, several clinical studies evaluating pazopanib in non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, soft tissue sarcoma (STS), cervical cancer, hepatocellular cancer (HCC), multiple myeloma (MM), and glioma are in progress or have been completed.

Clinical Efficacy

In a randomized, double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated subjects with advanced RCC, the median progression-free-survival (PFS) was significantly prolonged with pazopanib compared with placebo in the overall study population (9.2 vs. 4.2 months). The objective response rate (RR) was 30% with pazopanib and only 3% with placebo (28). In subjects with ovarian cancer, 31% of subjects experienced a CA-125 response to pazopanib, with a median time to response of 29 days and median duration of response of 113 days (Investigator's Brochure, 2010). Median PFS was 84 days and the overall RR was 18%. In advanced or metastatic STS, the rate of PFS at 12 weeks was 43.9% for leiomyosarcoma, 48.6% for synovial sarcoma, 26.3% for adipocytic sarcoma, and 39% for other types of sarcoma (29). In a phase 2 trial of subjects with early-stage NSCLC, 86% of subjects experienced a reduction in tumor volume after short-term, preoperative use of pazopanib (~2-6 weeks) as assessed by high-resolution CT scanning (30). Interim results from a phase 2 study of pazopanib in subjects with recurrent or metastatic breast invasive breast cancer showed that the clinical benefit rate was 26% (31). The median TTP was 3.7 months, and 50% of subjects with measurable target lesions had some decrease in size. PFS at 3 and 6 months was 55% and 28%, respectively. Preliminary results from a randomized study in subjects with first-line advanced ErbB2-positive advanced or metastatic breast cancer showed that a higher response rate (36.2% vs. 22.2%) was

observed in subjects on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared to monotherapy lapatanib 1500 mg once daily (32). In a randomized phase 2 study of pazopanib vs. lapatinib vs. the combination of pazopanib/lapatinib in advanced and recurrent cervical cancer, there was a 34% reduction in risk for progression in subjects receiving pazopanib relative to lapatinib. The median PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib group (33). Interim analysis of data from 26 subjects showed that pazopanib has both a favorable toxicity profile and promising clinical activity in subjects with advanced and progressive differentiated thyroid cancers (34). Five confirmed partial responses (PRs) (19%) were reported. Pazopanib has not shown efficacy in phase 2 studies conducted in MM or glioma (Investigator's Brochure, 2010)

Safety

The randomized, phase 3 study in mRCC subjects provided a key comparison of safety with pazopanib compared to placebo (28). The overall frequency of adverse events (AEs) reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). The most common AEs reported in >20% of subjects in the pazopanib arm were diarrhea (52%), hypertension (40%), hair color change (depigmentation; 38%), nausea (26%), anorexia (22%), and vomiting (21%). Most of the events were grade 1 or 2. A higher number of grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The most frequent grade 3 AEs in the pazopanib arm were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypertension, and diarrhea. The frequency of grade 4 and grade 5 AEs was similar between the pazopanib and placebo arms: grade 4 in 7% and 6%, respectively; grade 5 in 4% and 3%, respectively.

A comprehensive review of all completed and ongoing pazopanib clinical trials with a cut-off date of September 2009, lists 15 most commonly occurring serious AEs (SAEs) (Investigator's Brochure, 2010). Vomiting and diarrhea are the most commonly reported SAEs across all the pazopanib studies. As a consequence of this, dehydration is also seen with pazopanib treatment. For most reports, the AEs resolved after supportive treatment such as antiemetics, antidiarrheal agents, and IV fluids. GI perforation is commonly associated with VEGF pathway inhibitors. This may manifest as abdominal pain which is not uncommon in cancer subjects for many reasons. Of the 42 subjects in pazopanib trials with SAEs of abdominal pain, only three had a documented underlying intestinal perforation. In July 2006, the DCTD, NCI, issued an Action Letter to investigators using pazopanib describing the occurrence of bowel perforations in subjects on pazopanib clinical trials.

Dyspnea is also frequently seen in pazopanib-treated subjects and may reflect the underlying disease under treatment. Anemia is commonly seen in cancer subjects in association with chemotherapy, hemorrhage, or infection. The SAEs of pyrexia were attributed to multiple causes: concurrent infections, the underlying malignancy, hepatic events, other concomitant medications, and unknown causes. Hepatic events are thought to be on-target tyrosine kinase inhibitor (TKI) class effects, as hepatic enzyme elevations have been seen with other agents of this class. Careful clinical evaluation is, therefore, warranted in subjects with hepatic abnormalities. Pneumonia can be a complication of chemotherapy or can result from debilitation and advanced disease. Review of the 33 SAEs showed the presence of an underlying cause other

than pazopanib in 19 of the 30 subjects. Fatigue and asthenia are commonly reported and have multiple causes.

Hypertension observed with pazopanib is a known class effect. There have been 30 SAEs of hypertension and 3 SAEs of hypertensive crisis in pazopanib clinical trials. There were 28 subjects who were effectively treated with antihypertensive medication initiation or dose adjustment, while 4 had no such treatment. Although there were 29 SAEs of pleural effusion, the body of data does not suggest that any of these cases were due to pazopanib. There have been 24 SAEs of pulmonary embolism (PE) reported in pazopanib trials. This is of particular relevance since other members of this class have been associated with PE and other venous thromboembolic events.

In addition, there have been reports of cardiac and cerebral ischemic events, GI perforation or hemorrhage, pulmonary hemorrhage, cerebrovascular hemorrhage, QT prolongation, and Torsades de Pointes in pazopanib clinical trials.

Cases of hepatic failure, including fatalities, have been reported during the use of pazopanib. Two of 977 patients (0.2%) died with disease progression and hepatic failure in trials that supported the renal cell carcinoma (RCC) indication. One of 240 patients (0.4%) died of hepatic failure in the randomized soft tissue sarcoma (STS) trial. In RCC monotherapy trials using pazopanib, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported as very common (≥10%), and abnormal hepatic function and hyperbilirubinemia have been reported as common (≥1% to <10%) adverse reactions. In STS monotherapy trials using pazopanib, increased ALT and AST have been reported as common (≥1% to <10%) adverse reactions.

Elevated ALT (>3X ULN) and concurrent elevated ALT (>3X ULN) and bilirubin (>2X ULN) have been observed primarily between weeks 3 and 9 of therapy in pazopanib clinical trials. A comparison across trials with pazopanib indicates ALT >3X ULN in 1% and approximately 5% of treated patients at weeks 2 and 3, respectively. Most new cases of ALT >3X ULN occurred by week 9. More frequent monitoring between weeks 3 and 9 may lead to earlier detection of elevated serum liver tests and hepatotoxicity in patients taking pazopanib.

Clinical Pharmacokinetics

The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily (Investigator's Brochure, 2010). Increases in doses above 800 mg to 2000 mg, in the fasted state will not result in increased systemic exposure. Geometric mean pazopanib t½ values ranged from 18.1-52.3 hours. The mean t½ was 30.9 hours in the 800 mg once daily group, in phase 2 and 3 trials. Oral absorption is significantly enhanced when dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach, at least 1-2 hours after a meal.

Preliminary information on the pharmacokinetics (PK) of pazopanib administered in combination with lapatinib has been reported (35). Thirty-three subjects received doses of lapatinib ranging from 750-1500 mg once daily along with pazopanib at doses of 200-500 mg

daily. Preliminary mean plasma concentrations 24 hours after administration (C24) on day 22 were ~19 mcg/mL and 23 mcg/mL after pazopanib doses of 250 mg and 500 mg, respectively. These values are similar to the mean C24 values observed after administration of 800 mg pazopanib alone (23.1 mcg/mL). Plasma lapatinib concentrations at 750-1500 mg daily were similar to those observed after monotherapy. Concurrent administration of pazopanib and lapatinib was generally well tolerated; coadministration of lapatinib may alter the PK of pazopanib (Dejonge et al., 2006).

Preliminary PK information on the combination of pazopanib and paclitaxel administered to subjects with advanced cancer has been reported (36). Twelve subjects received paclitaxel (15-80 mg/m^2 on days 1, 8, and 15 every 28 days) and pazopanib at 400 or 800 mg/day starting on day 2 of the first cycle. Coadministration of pazopanib increased paclitaxel mean Cmax and AUC0-8 approximately 20-35% (36).

Age, body weight, gender, and race had no significant influence on pazopanib PK.

Potential Drug Interactions
Pazopanib is metabolized primarily by CYP3A4, and systemic exposure to pazopanib is altered by inhibitors and inducers of this enzyme. The concomitant use of strong CYP3A4 inhibitors should be avoided. If co-administration of a strong CYP3A4 inhibitor is warranted, a dose reduction to 400 mg is recommended. Grapefruit may also increase plasma concentrations of pazopanib and should be avoided. CYP3A4 inducers such as rifampicin may decrease plasma concentrations; therefore, an alternative concurrent medication with none or minimal enzyme induction should be used. Concommitant use of medications that have narrow therapeutic windows and that are substrates of CYP3A4, CYP2D6 or CYP2C8 should occur only with caution.

Concommitant medications that have narrow therapeutic windows ***and*** are substrates of CYP3A4, CYP2D6 or CYP2C8 should be used with caution. If possible, medications that are not substrates for these enzymes and/or do not have narrow therapeutic windows should be substituted.

2.3 ARQ 197

The c-MET RTK mediates the signals for a variety of physiological processes that have implications for oncogenesis, including migration, invasion, cell proliferation, and angiogenesis. A wide variety of human cancers exhibit constitutively dysregulated c-MET activity, either through over-expression of the c-MET kinase, activating mutations in c-MET, or increased autocrine or paracrine secretion of the c-MET ligand hepatocyte growth factor/scatter factor (HGF/SF). These alterations have been strongly implicated in tumor progression and metastasis in a variety of cancers, and a high constitutive activation of the c-MET RTK has been correlated with poor clinical prognosis.

c-MET can be activated in both a ligand-dependent manner, by the overexpression of c-MET and/or its ligand HGF, or a ligand-independent manner as in the case of activating mutations of c-MET such as those described in certain gastric carcinoma-derived cell lines. The cell line

MKN-45, has amplified *MET* gene in the absence of mutation and superabundance of MET protein at the cell surface, which is fully active in the complete absence of HGF. Activation and autophosphorylation of c-MET results in the binding and phosphorylation of adaptor proteins such as Gab1, Grb2, Shc and c-Cbl, and results in the subsequent activation of signaling pathways, including the PI3K/Akt, FAK, STAT and Ras/MEK/Erk pathways that play various roles in cell survival, proliferation, invasion, and angiogenesis. In the melanocyte lineage, c-MET expression is upregulated by microphthalmia-associated transcription factor (MITF), which has been implicated in the oncogenesis of melanoma and other cancers [20, 21]. The presence of c-MET in most cancers, and its role in controlling multiple signal transduction pathways involved in tumor growth render this enzyme a logical therapeutic target for human cancer.

ARQ 197 is a potent non-ATP competitive RTK inhibitor with high selectivity for the c-MET RTK, as determined by biochemical and cellular assays. ARQ 197 has growth inhibitory activity in breast, prostate, colon and pancreatic carcinoma xenograft models. ARQ 197 has also been shown to inhibit metastasis in a metastatic orthotopic colon cancer xenograft model [13, 22, 23]. A comprehensive review of ARQ 197 can be found in the ARQ 197 Investigator's Brochure (2010).

2.3.1 Nonclinical Pharmacology

***In Vitro* Efficacy**

ARQ 197 selectively inhibits the *in vitro* biochemical activity of recombinant c-MET with a K_i of approximately 355 nM. The potency of ARQ 197 inhibition of c-MET activity was independent of ATP concentration, suggesting that the mode of inhibition of ARQ 197 is of a non-competitive nature. While ARQ 197 inhibits c-MET kinase activity, it is not a promiscuous kinase inhibitor. When ARQ 197 was profiled against 230 protein kinases at a nominal concentration of 5 or 10 μM, ARQ 197 inhibited only 4 protein kinases greater than 20%. These data suggest that ARQ 197 is a highly selective c-MET kinase inhibitor.

In cell-based kinase assays, ARQ 197 inhibited HGF-induced activation of c-MET (gauged by autophosphorylation) with an IC_{50} between 0.1–0.5 μM in multiple human cancer cell lines. This suppression was effective for at least 8 to 12 hours after withdrawal of ARQ 197, demonstrating a sustained durability of c-MET inhibition by ARQ 197. Furthermore, ARQ 197 decreased phosphorylation of most of the c-MET downstream effectors including FAK, STAT-3, Erk-1 and Erk-2, but not Akt. This suggests that, through c-MET inhibition, ARQ 197 also induces a decrease in the phosphorylation and activation of many downstream targets in the pathways served by this oncogenic kinase.

ARQ 197 showed broad-spectrum *in vitro* anticancer activity against human tumor lines, including those derived from breast, pancreas, colon, gastric, and lung. The potency of ARQ 197 in cancer cells expressing detectable c-MET ranges from 0.1–0.6 μM. By contrast, human cells lacking or minimally expressing c-MET such as NCI-H661 (non-small cell lung cancer; NSCLC) and NCI-H446 (small cell lung cancer) yielded IC_{50} values approximately 10-fold higher, indicating a correlation between the presence of c-

MET and the sensitivity of the cells towards ARQ 197. The ability of ARQ 197 to inhibit c-MET phosphorylation correlates with its ability to inhibit growth and induce apoptosis in c-MET expressing cancer cells.

Overexpression of c-MET correlates with tumor cell migration and invasiveness, and invasion assays demonstrated that ARQ 197 potently inhibited invasion in c-MET expressing tumor cell lines (IC_{50}s of approximately 0.3–0.45 μM), but less so in non-c-MET expressing lines (IC_{50} = 5.4 μM). In a wound healing assay, ARQ 197 also inhibited migration of NCI-H441 cells (human lung adenocarcinoma) in response to HGF. Overall, these results indicate that ARQ 197 has anticancer activity, an effect which is mediated via c-MET inhibition.

Another study assessed a panel of 64 human cancer cell lines encompassing a spectrum of genotypes and tissue origins. The combination of ARQ 197 and sorafenib showed synergistic cytotoxicity in nine cell lines, including three NSCLC cell lines, two breast cancer cell lines, a melanoma cell line, a renal clear cell carcinoma cell line, a cervical carcinoma cell line, and a squamous cell carcinoma cell line. An additive effect was seen with the ARQ 197/sorafenib combination across a wide range of 40 human cancer cell lines including, but not limited to, 5 colon cancer lines, 5 breast cancer cell lines, 4 additional NSCLC cell lines, and 3 hepatocellular carcinomas (HCC).

***In Vivo* Efficacy**

When administered via daily oral dosing, ARQ 197 was efficacious against multiple human cancer xenograft models. Beginning at a dose level of 200 mg/kg, tumor growth inhibition was seen in breast (79%), colon (39%), pancreatic (58%), prostate (72%), and gastric (52%) models. Increasing the dose to 300 mg/kg improved tumor inhibition in colon (55%), pancreatic (60%), and prostate (77%) models. ARQ 197 was well tolerated in these studies with no drug related clinical signs or deaths. There was no significant change in body weight at any of the dose levels tested. Furthermore, the antitumor activity of ARQ 197 is accompanied by the ablation of c-MET activity, as assessed by the decreased level of phosphorylated c-MET in the dissected xenograft tumor tissue. This suggests a potential mechanism-based clinical biomarker.

A study conducted with the NCI-H522 NSCLC cell line suggests that antitumor effects of ARQ 197 and sorafenib were modestly additive in human tumor xenograft models. The combination was well tolerated, with no body weight changes or deaths observed.

Nonclinical Pharmacokinetics

The pharmacokinetics of ARQ 197 were evaluated and compared in mice, rats, and dogs using different dosing routes, levels, and formulations. In general, exposure to ARQ 197 increased as the dose was increased. Overall, the corresponding increases in $AUC_{0\text{-}inf}$ and C_{max} were not dose proportional. The $t_{1/2}$ of ARQ 197 generally ranged from 1–4.5 hours across all studies and all species, though there were some exceptions. For instance, rats displayed a highly variable $t_{1/2}$ (1.48 – 37.8 hours), the reason for which is unknown. Bioavailability after single dosing was somewhat variable between species: 16-35% in rats, 33-60% in dogs, and 21-37% in mice. After multiple dosing in 7- day, 28- day, 8-

week, and 26- week studies, there were no consistent changes in C_{max} and AUC values in rat or dog, indicating no marked accumulation of ARQ 197.

Metabolism
Mass balance and tissue distribution studies indicated that the primary route of elimination of ARQ 197 is fecal and that ARQ 197 generally did not accumulate (after 96 hours) in any of the tissues tested. Data from *in vitro* metabolism studies suggest that ARQ 197 is relatively stable in human liver microsomes with a $t_{1/2}$ of 29 min. The $t_{1/2}$ of ARQ 197 in male dog liver microsomes was similar to that of human liver microsomes with a $t_{1/2}$ of 29 min ($t_{1/2}$ in female dog liver microsomes was 20.5 min).

From studies conducted with individual CYP P450 isozymes, ARQ 197 was rapidly metabolized by CYP2C19 ($t_{1/2}$ = 2.83 min) and moderately metabolized by CYP 3A4 ($t_{1/2}$ = 16.3 min). The $t_{1/2}$ values for the other CYP P450s (1A2, 2C9, 2D6, and 2C8) tested were all greater than 27.4 min. Drugs which affect the activity of CYP2C19 or CYP3A4 may markedly alter the plasma concentration of ARQ 197. The IC_{50} of ARQ 197 was evaluated for each CYP 450 isoform (1A2, 2C8, 2C9, 2C19, 2E1 and 3A4), and all were greater than 10 μM.

Nonclinical Toxicology
Preclinical toxicity for ARQ 197 was assessed in the rat and beagle dog in single and repeat dose studies of up to 26 weeks in duration. In 28-day repeat-dose studies, clinical pathology signs typically observed at the high dose (45 mg/kg) included lower red cell mass, lower absolute reticulocyte count, and lower absolute neutrophil and monocyte counts for males and females. In addition, females had lower absolute lymphocyte and eosinophil counts. Microscopic findings at high doses included depletion of lymphocytes in the thymus, femur and sternum bone marrow depletion, and hypertrophy and vacuolation in peripherolobular hepatocytes. Importantly, these clinical and anatomic pathology findings were reversed by 2 weeks after cessation of dosing.

2.3.2 Clinical Experience

The pharmacokinetics, metabolism, safety, and efficacy of ARQ 197 have been investigated in multiple phase 1 and 2 clinical trials in cancer patients. Two phase 1 dose escalation trials (ARQ 197-101 and ARQ 197-103) have defined the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for continuous doses of ARQ 197 as a single agent. Another phase 1 study (ARQ 197-111) evaluated the MTD and RP2D of ARQ 197 administered in combination with erlotinib on a continuous schedule. Additional ongoing phase 1 and phase 1/2 trials evaluating ARQ 197 include ARQ 197-114 (monotherapy in HCC); ARQ 197-116 (combination with sorafenib); and ARQ 197-117 (combination with gemcitabine).

In addition, there are two active phase 2 clinical trials: ARQ 197-204 is evaluating the efficacy of ARQ 197 in patients with MITF-associated tumors, while ARQ 197-209 is an ongoing global, randomized, placebo controlled, double-blind phase 2 trial comparing

treatment with erlotinib plus ARQ 197 versus treatment with erlotinib plus placebo in patients with previously treated NSCLC.

Clinical experience to date suggests that ARQ 197 has a favorable safety profile [23]. Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2010). Safety and efficacy results are summarized below.

Phase 1 Studies
Studies **ARQ 197-101** and **ARQ 197-103** were phase 1 dose escalation trials of ARQ 197 in adult patients with locally advanced or metastatic solid tumors. In ARQ 197-101 trial, 13 dose levels ranged from 10–360 mg BID and 2 dosing schedules (intermittent versus continuous) were explored and no dose-limiting toxicities (DLTs) were reported at doses below 360 mg BID. In ARQ 197-103 trial, ARQ 197 was given twice daily continuously and the MTD was found to be 360 mg BID. The most common drug-related adverse events (AEs; ≥5% and ≥2 events) seen in these studies were fatigue (13.9% and 15.7%, respectively), nausea (13.9%, 13.7%), vomiting (10.1%, 11.8%), and diarrhea (6.3%, 7.8%). Serious adverse events (SAEs) reported at a >3% incidence were disease progression, dehydration, anemia, nausea, renal failure acute, and vomiting, febrile neutropenia.

Study **ARQ 197-114** is an ongoing safety study of ARQ 197 in cirrhotic subjects with HCC. ARQ 197 is administered continuously at a dose level of 360 mg BID. The most common drug-related AEs (≥5% and ≥2 events) are asthenia (47.6%), neutropenia (42.9%), anemia (42.9%), leukopenia (38.1%), anorexia (38.1%), diarrhea (28.6%), alopecia (19.0%), thrombocytopenia (14.3%), vomiting (14.3%), hepatobiliary disorders (14.3%), hyperbilirubinemia (14.3%), lymphopenia (9.5%), bradycardia (9.5%), dysgeusia (9.5%), and oropharyngeal pain (9.5%). Drug-related SAEs leading to discontinuation from the study include three cases of neutropenia.

Study **ARQ 197-111** is an ongoing phase 1 dose escalation trial of ARQ 197 administered in combination with erlotinib in adult patients with advanced solid tumors. A dose of 360 mg ARQ 197 BID in combination with erlotinib 150 mg daily has been identified as the RP2D (one DLT of neutropenia). The most commonly-reported drug-related AE in this study was bradycardia, with 15 episodes reported in 4 patients; these events were generally mild and asymptomatic (grade 1), and 14 of these events occurred at the 360 mg BID dose level of ARQ 197.

Phase 2 Studies
Protocol **ARQ 197-204** is a phase 2 study of ARQ 197 in patients with MITF-associated tumors, including translocation-associated renal cell carcinoma (t-RCC), alveolar soft-part sarcoma (ASPS), and clear-cell sarcoma (CCS). The initially enrolled patients received 120 mg ARQ 197 BID; patients enrolled after the RP2D was determined (in ARQ 197-103) received 360 mg ARQ 197 BID. Among 47 patients treated in this study, ARQ 197 demonstrated a favorable safety profile and was well tolerated at both doses. The most common (≥5% and ≥2 events) drug-related AEs were fatigue, pyrexia, nausea,

vomiting, diarrhea, retching, anemia, lymphopenia, pain in extremity, anorexia, headache, insomnia, dyspnea, cough, neutrophil count decreased, decreased white blood cell count, increased alanine aminotransferase level, increased aspartate aminotransferase level, decreased hemoglobin level, sinus bradycardia, and rash. To date, 45 patients are evaluable for efficacy. One patient with CCS demonstrated a confirmed PR. Twenty-seven patients demonstrated SD, including 21 with ASPS, three with t-RCC, and three with CCS. Overall, 12 subjects have had SD for $\geq$24 weeks. Currently, two phase 2 trials are ongoing; ARQ 197 plus erlotinib versus ARQ 197 plus placebo in patients with previously treated NSCLC (**ARQ 197-209**) and single agent ARQ 197 in patients with HCC (**ARQ 197-215**).

Pharmacokinetics
Approximately 345 subjects with cancer and over 100 healthy subjects participated in phase 1 studies of ARQ 197. Clinical PK data are available from multiple clinical studies using ARQ 197 as either the amorphous solid or 1 of 2 crystalline forms designated form A or form B. Overall, following oral administration ARQ 197 is moderately absorbed with a T_{max} ranging from 2–6 hours. In general, ARQ 197 exposure increases with increases in dose; however, exposure is not dose proportional. There is wide intersubject variability in ARQ 197 PK. Based on population pharmacokinetic (PopPK) analysis, this variability is partly due to CYP2C19 polymorphism, fed status during ARQ 197 administration, ARQ 197 form (amorphous versus crystalline A versus crystalline B), and also possibly ethnicity differences (Caucasian versus Japanese).

In vitro human liver microsome studies indicate involvement of both CYP2C19 and cytochrome P450 3A4 (CYP3A4) in ARQ 197 metabolism. In humans, ARQ 197 showed a genotype exposure relationship dictated mainly by CYP2C19 genotype. In healthy subjects, CYP2C19 poor metabolizers (PMs) had much higher exposure than extensive metabolizers (EMs), as reflected by $AUC_{0\text{-}48}$ and C_{max} (11-fold and 3-fold higher, respectively) and lower clearance (mean of 2.4 L/h versus mean of 33.9 L/h). However, based on steady state exposure data in cancer subjects the PM exposure ($AUC_{0\text{-}12}$) is only 1.4- to 4-fold greater than EM exposure. Hence, differences in CYP2C19 metabolism will contribute to variability in PK between subjects. In a phase 1 dose-escalation study, 10 of 43 patients were characterized as PMs. Additional studies comparing the PK of the amorphous form of ARQ 197 to the crystalline forms A and B of ARQ 197 showed that the amorphous form of ARQ 197 resulted in higher exposure (C_{max}, AUC) than either crystalline form A or B. Specifically, C_{max} was approximately 60% to 70% lower for forms A and B, respectively, compared with the amorphous form. Similarly, AUC was 20% to 30% lower for crystalline forms A and B, respectively, relative to the amorphous form.

When ARQ 197 was administered immediately after a high-fat meal to healthy subjects, the exposure was 3 times greater than the exposure under fasted conditions (fasted versus fed: $AUC_{0\text{-}last}$, 4858 $\pm$1793 ng/hr/mL versus 13356 $\pm$5385 ng/hr/mL and $AUC_{0\text{-}inf}$, 6166 $\pm$2393 versus 13558 $\pm$6397 ng/hr/mL). However, the observed exposure under fed conditions was similar to that observed in the prior clinical studies in subjects with cancer and less than the MTD exposure. Additionally, in cancer subjects (study ARQ 197-117),

the exposure when ARQ 197 crystalline B was administered 360 mg BID (the phase 3 dose) under fed versus fasting (at least 1 hour before and 2 hours after a meal) condition were similar (fed versus fasting: 12251 versus 10453 ng/hr/mL). Furthermore, when administered under fed conditions, the variability in ARQ 197 exposure is generally lower compared with the fasted condition.

2.4 Correlative Studies Background

2.4.1 Measurement of MET in tumor biopsies by immunoassay

Serial evaluation of the tumor biopsy samples will be performed with quantitative sandwich chemiluminescence immunoassays to measure drug effect on modulation of intact c-MET and 2 known key domains in intact c-MET: the tyrosine kinase (TK) domain and the C-terminal signaling/mediator docking domain (multiple docking site). Phosphorylation status of tyrosine at positions 1235 and 1356 denotes the activation state of the TK domain and multiple docking site, respectively. Three quantitative ELISA-based immunoassay for the measurement of c-MET (intact MET) and two c-MET phosphorylated isoforms (pY1235 and pY1356) have been developed in the laboratory of Dr. Apurva Srivastava, SAIC-Frederick, and are currently under validation for use to assess target modulation. The amount of intact MET serves as a denominator to determine the fraction of MET phosphorylated at either pY1235 or pY1356. Assay readout is based on relative light units from a Tecan luminometer after addition of chemiluminescent substrate. Six quantitative MET standards over a 30-fold range are loaded into a plate along with testing samples for calculating the MET values. Two assay controls (low-C and High-C) are included in each run plate to monitor consistency of the assay. Manuscripts describing these assays are in preparation.

Analytical validation and fit-for-purpose modeling in preclinical studies are currently underway. Preliminary results indicate adequate analytical performance, and >60% inhibition in phosphorylation of Y1235 within 4 hours of treatment with two selective c-MET inhibitors, as compared to the vehicle-treated group. Intra-tumor variability of c-MET was 18-37% in biopsy specimens among vehicle treated groups.

Sequencing for known mutations in the MET kinase and ligand binding domains will also be performed in tumor biopsies.

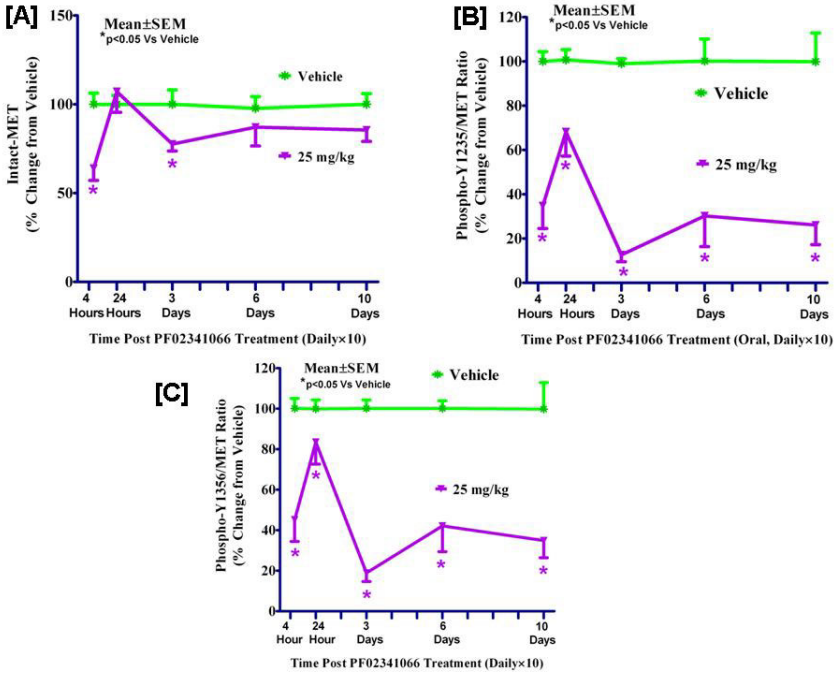

Figure 5: Inhibition of MET and pMET after treatment with the MET inhibitor PF02341066 over a period of 10 days. Drug was given daily for 10 days and biopsies were collected 4 hours after each dose on days 1, 3, 6, 8 and 10. At the 25 mg/kg dose, mean intra-tumor MET levels (A) were significantly lower on day 1 and day 3. However, mean intra-tumor levels of normalized pY1235 MET (B) and pY1356 MET (C) were consistently lower (50-80%) in treated mice on days 3, 6, 8, and 10, as compared to pMET levels in vehicle treated group.

2.4.1.1 Measurement of MET/phospho-MET

With Amendment D (12/7/2012), the primary study objective dealing with biomarker endpoints was revised from determining reduction of phospho-MET in tumor biopsy samples following administration of ARQ 197 in light of preclinical findings and published observations about ARQ 197's mechanism of action. Data suggest that ARQ 197 blocks MET by locking the inactive conformation of MET, thus preventing further activation [24]. In contrast, ARQ 197's effects on constitutively phosphorylated Y1234/35 MET are unclear [25]. We tested ARQ 197 modulation of phospho-MET in gastric tumor xenograft models with constitutively active c-MET (SNU5 and MKN45) [26]. ARQ 197 administered at doses of 200-400 mg/kg/day did not significantly change phospho-MET levels in either the SNU5 or MKN45 model (Figure 6); however, when ARQ 197 was co-administered with pazopanib in the SNU5 model, ARQ 197 prevented pazopanib-induced activation of phospho-MET (Figure 6A and 6B). These results generally support the hypothesis underlying combination clinical trials of VEGFR and MET inhibitors [27], specifically, that ARQ 197 treatment reverses MET activation by pazopanib.

Unfortunately, the mechanism by which ARQ 197 prevents adaptive response to VEGFR inhibition could not be verified by the phospho-MET biomarker response. Therefore, the objectives of this trial were modified to address evaluation of phospho-MET as an exploratory biomarker for MET activation by pazopanib and subsequent blunting of pazopanib-induced activation of MET by ARQ 197. The study design was revised to support this objective. The number of cohorts in the expansion phase was reduced from 3 to 2 as the originally planned cohort with a 7-day single-agent ARQ 197 lead-in will be less informative and of less potential benefit to patients. Confirmation of MET expression by immunohistochemistry in archival tissue is no longer an eligibility criterion for the expansion phase; MET and pMET levels will be determined from on-study biopsies only, thus expansion–phase eligibility is now open to patients with refractory advanced solid tumors rather than MET-expressing malignancies.

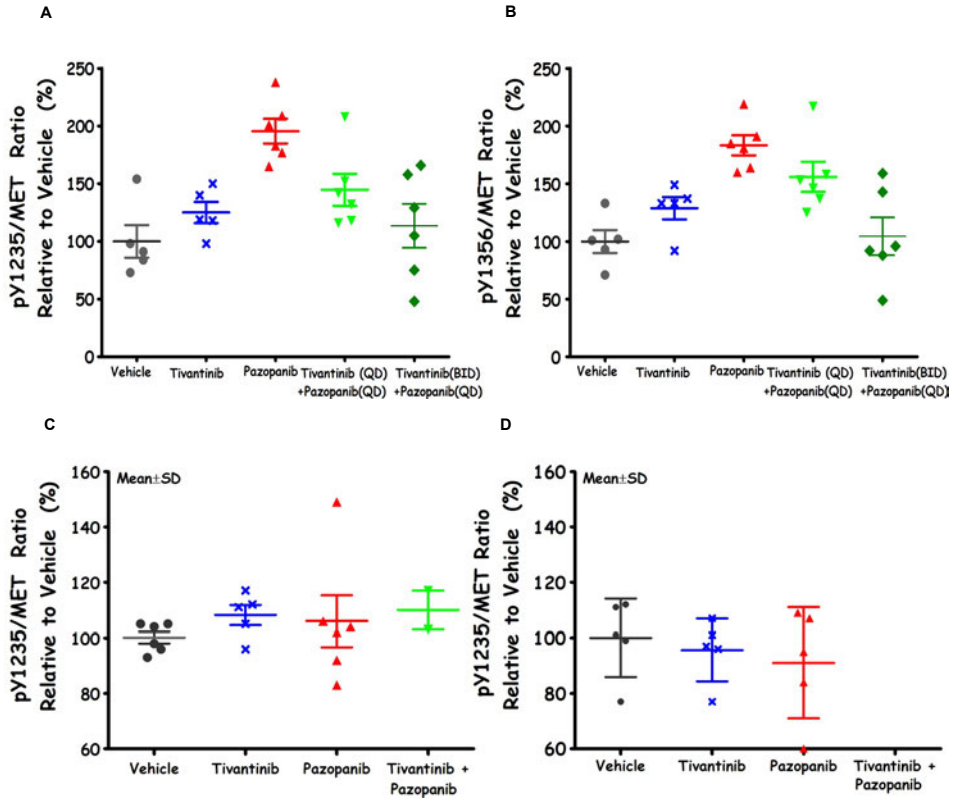

Figure 6 (**A** and **B**) Treatment of SNU5 xenograft biopsy specimens with ARQ 197 (200 mg/kg/day QD and 400 mg/kg/day BID) alone did not significantly change total MET, pY1235-MET, or pY1356-MET levels compared to vehicle. In contrast, pazopanib (100 mg/kg) significantly increased the pY1235-MET/MET ratio (**A**) and the pY1356-MET/MET ratio at 4-hours (**B**) after the day 8 dose compared to vehicle. This increase was inhibited when pazopanib was administered in combination with ARQ 197 ($p<0.05$). (**C** and **D**). In the MKN45 xenograft model, biopsy specimens did not show any significant changes in the pY1235-MET/MET ratio compared to vehicle in any treatment regimen (**C** – 4 hr; **D** – 10 hr after treatment on day 8). Intact MET was significantly lower in the combination group compared to vehicle ($p<0.05$). Most of the needle biopsy

specimens from the combination groups were not evaluable because they did not yield detectable levels of intact MET.

Note: with Amendment I (v3/4/14), co-administration of pazopanib and ARQ 197 continuously was removed from the study prior to accruning patients to this cohort.

2.4.2 Assessment of HIF-1α protein expression in tumor biopsies by ELISA

The basis for this study is that anti-VEGF therapy increases intratumoral hypoxia by causing vascular regression, leading to increased expression of hypoxia-inducible factor–1α (HIF-1α). HIF-1α plays a central role in tumor progression by acting as master regulator of how cancer cells adapt to hypoxic conditions. One reason postulated for the limited efficacy of anti-angiogenic and anti-VEGF agents is that they cause intra-tumoral hypoxia, resulting in the induction and up-regulation of hypoxia-inducible factors (HIF) such as HIF-1α. To determine whether the combination of MET inhibitor and anti-VEGF therapy modulates intra-tumoral levels of HIF-1α expression, we will analyze tumor biopsies using an ELISA that has been validated by the PADIS laboratory (Dr. Bob Kinders) at Frederick National Laboratory for Cancer Research. The assay detected 4-fold higher levels of HIF-1α in PC-3 cells cultured under hypoxic conditions than those cultured under normoxic conditions (Table 1). Spike-and-recovery experiments during assay validation revealed assay accuracy higher than 99% (Figure 8).

2.4.3 Circulating levels of HGF, soluble MET (sMET), VEGF-A, and soluble VEGFR2 (sVEGFR2) in patients treated with MET and VEGFR inhibitors

Many proteins are proteolytically released from the cell surface by a process known as ectodomain shedding. Shedding occurs under normal physiologic conditions and can be increased in certain pathologies. MET is among the many receptors for which ectodomain shedding has been demonstrated. HGF stimulates mitogenesis, motogenesis, and morphogenesis in a variety of cellular targets during development, homeostasis and tissue regeneration. Inappropriate HGF signaling resulting in unregulated cell proliferation, motility, and invasion occurs in several human malignancies. This can occur through paracrine signaling, autocrine loop formation, receptor mutation, gene amplification or gene rearrangement accompanied frequently with overexpression of ligand and/or receptor proteins. Working under the hypothesis that aberrant MET pathway activation in cancer might result in increased ectodomain shedding MET could be a useful biomarker of tumor progression, Athauda et al. developed a sensitive electrochemiluminescent immunoassay to quantitate MET protein in biological samples [29]. Their study showed significant direct correlations between malignant potential and sMET production in tumor-derived and genetically engineered cell lines, and between tumor burden and plasma sMET levels in mice harboring human tumor xenografts [29]. These preclinical studies supported the hypothesis that sMET might indicate malignant potential and/or tumor burden for cancers where the pathway is active.

Several studies of human clinical samples are now underway to investigate the potential utility of sMET to aid diagnosis and patient selection, and as a pharmacodynamic marker for drugs that directly target MET kinase activity. Among these is an ongoing collaboration between GlaxoSmithKline (GSK) and the NCI Urologic Oncology Branch to measure plasma sMET, HGF, VEGF-A and sVEGFR2 in patients in Phase I and II clinical trials of GSK1363089 (GSK'089), an inhibitor of MET and VEGFR2 tyrosine kinases. In a Phase II gastric cancer study, patients treated with GSK'089 on an intermittent dosing schedule showed significantly increased plasma sMET and VEGF-A during the treatment periods and decreases during drug holidays. Follow-up cell-based studies show that inhibition of MET kinase activity blocks receptor internalization, resulting in increased exposure to cell surface MET sheddase(s), suggesting a direct short-term relationship between sMET levels and drug target inhibition. Increased VEGF-A levels have been reported as a response to VEGFR inhibitors in previous clinical studies. Median tumor burden did not change significantly over the course of the gastric study, so it was not possible to determine whether sMET levels could also reflect tumor burden. This question will be better assessed in an ongoing Phase II clinical trial of GSK'089 in patients with papillary renal cell carcinoma, where changes in tumor burden meeting RECIST criteria were reported in an interim trial report [30].

2.4.4 Pharmacogenetic (PG) assessment of CYP2C19 in patients treated with ARQ 197

ARQ 197 is metabolized mainly by CYP2C19. As described earlier in this section, there is wide inter-subject variability in ARQ 197 PK. Based on population pharmacokinetic analysis, this variability is partly due to CYP 2C19 polymorphism, fed status during ARQ 197 administration, ARQ 197 form (amorphous versus Crystalline A versus Crystalline B), and also possibly ethnicity differences (Caucasian versus Japanese). In healthy subjects, CYP 2C19 poor metabolizers (PMs) had much higher exposure than extensive metabolizers (EMs), as reflected by AUC0-48 and Cmax (11-fold and 3-fold higher, respectively) and lower clearance (mean of 2.4 L/h versus mean of 33.9 L/h). However, based on steady state exposure data in cancer subjects, the PM exposure is only 1.4 to 4-fold greater than EM exposure. Hence, differences in CYP 2C19 metabolism will contribute to variability in PK between subjects. As a part of this study, a blood sample at screening will be taken to evaluate the CYP2C19 genotype of subjects. The sample will be analyzed only for genes involved in the pharmacokinetics, safety, and efficacy of ARQ 197. It will provide information on how individuals metabolize and react to the study medication. This information may be useful in increasing the knowledge of differences among individuals in the way they metabolize the study medication as well as helping in the development of new drugs or improvement of existing drugs.

2.5 Rationale

We hypothesize that co-administration of the MET inhibitor ARQ 197 will prevent the adaptive response to hypoxia resulting from treatment with the VEGFR inhibitor pazopanib, and conversely, that co-administration of pazopanib will prevent the effect of increased VEGF and reduced TSP-1 in tumors after treatment with ARQ 197. Therefore, the combination of these agents may result in improved antitumor effects.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically confirmed (by the Laboratory of Pathology, NIH) solid tumors that have progressed following at least one line of standard therapy or for whom no standard treatment options exist.

3.1.2 Patients must have measurable or evaluable disease.

3.1.3 Patients enrolling in the expansion cohorts must have disease amenable to biopsy, and be willing to undergo pre-and post-treatment biopsies.

3.1.4 Patients must have completed any chemotherapy, radiation therapy, or biologic therapy ≥ 4 weeks prior to entering the study (6 weeks for nitrosoureas or mitomycin C). Patients must be ≥ 2 weeks since any prior administration of a study drug in a phase 0 or equivalent study. Patients must have recovered to

eligibility levels from prior toxicity or adverse events. Treatment with bisphosphonates is permitted.

3.1.5 Patients who have had prior treatment with any anti-angiogenic therapy and/or c-MET inhibitor are eligible in the dose escalation phase unless the anti-angiogenic therapy and/or c-MET inhibitor were administered within the 4 weeks prior to entering the study. In the expansion phase, prior c-MET inhibitor is not allowed, and anti-angiogenic therapy is not allowed within the 3 months prior to entering the study.

3.1.6 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of pazopanib in combination with ARQ 197 in patients < 18 years of age, children are excluded from this study.

3.1.7 Life expectancy > 3 months.

3.1.8 ECOG performance status 0 or 1 (see Appendix A).

3.1.9 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count	≥1,500/μL
- Platelets	≥100,000/μL
- Total bilirubin	≤1.5 X institutional ULN
- AST (SGOT)/ALT (SGPT)	≤2.5 X institutional ULN
- Creatinine	≤1.5 mg/dL (133 mcmol/L); OR
- Measured creatinine clearance	≥60 mL/minute for patients with creatinine levels >1.5 mg/dL
- Urine protein/creatinine ratio	<1 OR 24-hour urine protein <1 gram

Subjects who have <u>both</u> bilirubin >ULN and AST/ALT >ULN are not eligible.

3.1.10 Subjects in the expansion cohort must have PT/INR/PTT ≤ 1.2 X institutional ULN, except patients with confirmed positive lupus anticoagulant test.

3.1.11 Subjects must have blood pressure (BP) no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry provided that the average of three BP readings at a visit prior to enrollment is less than 140/90 mmHg.

3.1.12 The effects of study drugs on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 2 months after dosing with study drugs ceases. Should a woman become pregnant or suspect she

is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Women of child-bearing potential must have a negative pregnancy test prior to entry.

3.1.13 Patients must be able to swallow whole tablets or capsules. Nasogastric or G-tube administration is not allowed.

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

3.2 Exclusion Criteria

3.2.1 Patients who are receiving any other investigational agents.

3.2.2 Patients with active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients whose brain metastatic disease status has remained stable for ≥ 4 weeks following treatment of the brain metastases are eligible to participate.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib or ARQ 197.

3.2.4 Eligibility of subjects receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of pazopanib or ARQ 197 will be determined following review of their cases by the Principal Investigator (see Sections 3.2.5-3.2.6 for further information). Efforts should be made to switch subjects with gliomas or brain metastases who are taking enzyme-inducing anticonvulsant agents to other medications.

3.2.5 Certain medications that act through the CYP450 system are specifically prohibited in subjects receiving pazopanib and ARQ 197 and others should be avoided or administered with extreme caution.

- **Strong inhibitors of CYP3A4** such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinivir, retonavir, saquinavir, telithromycin, voriconazole may increase pazopanib concentrations and **are prohibited; although, in exceptional circumstances they may be administered in conjunction with lowering the dose of pazopanib by 50%** of what would otherwise be administered. Grapefruit juice is also an inhibitor of CYP450 and should not be taken with pazopanib.

- **Strong inducers of CYP3A4,** such as rifampin, may decrease pazopanib concentrations, **are strictly prohibited.** (See Appendix B)

- **Medications which have narrow therapeutic windows and are substrates of CYP3A4, CYP2D6, or CYP2C8** should be avoided and, if necessary, administered **with caution.** (See Appendix B)

- **Inhibitors or inducers of CYP2C19** should be avoided and, if necessary, administered **with caution.** (See Appendix B)

3.2.6 Cardiovascular baseline QTc ≥ 480 msec will exclude patients from entry on study. Medications that may cause QTc interval prolongation are listed in Appendix C, and should be avoided by patients entering on trial. Patients for whom a given medication that may cause QTc interval prolongation cannot be discontinued may be eligible at the discretion of the study PI. A comprehensive list of agents with the potential to cause QTc prolongation can be found at http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm. (Note: If subjects must take medications with a risk or possible risk of Torsades de Pointes, they should be watched carefully for symptoms of Torsades de Pointes, such as syncope. Performing additional EKGs on subjects who must take one or more of these medications is not required; however, additional investigations, including EKGs, may be performed as per the treating physician's judgment.)

3.2.7 Subjects with any of the following cardiovascular conditions within the past 6 months:

- cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- clinically significant bradycardia or other uncontrolled cardiac arrhythmia
- admission for unstable angina or myocardial infarction
- cardiac angioplasty or stenting
- coronary artery bypass graft surgery
- pulmonary embolism, untreated deep venous thrombosis (DVT) or DVT which has been treated with therapeutic anticoagulation for less than 6 weeks
- arterial thrombosis
- symptomatic peripheral vascular disease
- Class III or IV heart failure as defined by the NYHA functional classification system (see Appendix D). A subject who has a history of Class II heart failure and is asymptomatic on treatment may be considered eligible

3.2.8 History of serious or non-healing wound, ulcer, or bone fracture.

3.2.9 Patients who received major surgery within the past 4 weeks

3.2.10 Subjects with any condition that may impair the ability to swallow or absorb oral medications/investigational product including:

- any lesion, whether induced by tumor, radiation or other conditions, which makes it difficult to swallow capsules or pills
- prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel
- active peptic ulcer disease
- malabsorption syndrome

3.2.11 Subjects with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including

- active peptic ulcer disease
- known intraluminal metastatic lesions
- inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal conditions which increase the risk of perforation
- history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to beginning study treatment

3.2.12 History of hemoptysis in excess of 2.5 mL (1/2 teaspoon) within 8 weeks prior to first dose of study drug.

3.2.13 Urine protein/creatinine ratio should be screened by urine analysis. If protein is 1+ or higher, 24-hour urine protein should be obtained and the level should be < 1 g for patient enrollment. Patients with < 1+ proteinuria are eligible following initial determination by urinalysis within 1 week prior to enrollment and do not need the urinalysis repeated.

3.2.14 Patients with clinically significant intercurrent illnesses, including but not limited to, life threatening infection, psychiatric illness/social situations that would limit compliance with study requirements will not be eligible to participate.

3.2.15 Pregnant women are excluded from this study because the effects of the study drugs on the developing fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the study drugs, breastfeeding should be discontinued prior to the first dose of study drug and women should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

3.2.16 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions.

3.2.17 Patients who require use of coumarin-derivative anticoagulants such as warfarin are excluded. Low molecular weight heparin is permitted for prophylactic use, but not therapeutic use.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Screening Evaluation

3.4.1 Histologic confirmation: By the Laboratory of Pathology, NIH. A block or stained slides of primary tumor tissue or of known recurrence will be required from each participant to confirm diagnosis.

3.4.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, performance score, EKG) will be conducted within 72 hours week prior to enrollment. Echocardiogram or MUGA scan for assessment of LV ejection fraction will be performed within 4 weeks prior to enrollment.

3.4.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI or CT scan with contrast of the brain, MRI liver, MRI for other disease sites, or bone scan may be done as clinically indicated.

3.4.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 72 hours prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, total protein, SGOT[AST], SGPT[ALT], magnesium, potassium, and sodium.
- Coagulation Profile: PT, PTT, INR
- Serum or urine pregnancy test for female participants of childbearing potential.
- Urinalysis for urine protein/creatinine ratio or 24-hour urine for proteinuria if patients have 1+ or greater urine protein/creatinine ratio.
- Serum liver tests (AST, ALT, serum bilirubin) will be performed as part of a risk mitigation plan before initiation of treatment with pazopanib.

4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to [redacted]. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note that it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

Off-Study Procedure: Authorized staff must notify the Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to [redacted].

5 TREATMENT PLAN

This is an open-label Phase I trial evaluating the combination of pazopanib, an oral VEGFR inhibitor, and ARQ 197, an oral MET inhibitor, in patients with refractory advanced solid tumors. Reported adverse events and potential risks for pazopanib and ARQ 197 are described in Section 7. Appropriate dose modifications for pazopanib and ARQ 197 are described in Section 6. No investigational or commercial agents or therapies other than pazopanib and ARQ 197 may be administered with the intent to treat the patient's malignancy.

The study will be carried out in 2 phases, as described in Section 5.1. The drugs will be administered in 28-day cycles (± 1 day for scheduling). Pazopanib tablets should be administered orally without food (at least 1 hour before or 2 hours after eating) once a day. ARQ 197 tablets should be administered orally with food twice daily approximately every 12 hours. A missed or vomited dose should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time. Patients will be asked to maintain a Study Medication Diary (Appendix E) and record each dose of medication. Patients will be given instructions for completing the medication diary and will be asked to return it to the clinic staff at the end of each cycle.

With Amendment H, dated 09/26/2013: For patients who have been on study for six or more cycles and are tolerating treatment well, two months worth of drug may be dispensed at a time; labs and blood pressure monitoring will only be performed once every 2 cycles (every 2 months). More frequent labs and assessment can be performed as clinically indicated.

History and physical examination can be done up to 3 days before start of a new cycle. Patients will be examined on D1, D8 (only for patients who will have tumor biopsy), and D15 in the dose escalation phase, or D1 and D8 in the expansion phase, at the clinical center for the first cycle and prior to every new cycle. Blood pressure (BP) will be checked every 2 weeks during the first 2 cycles in the dose escalation phase and on D1 and D8 of cycle 1 in the expansion phase, and then at the beginning of subsequent cycles. Mid-cycle blood pressure monitoring can be performed by any healthcare provider.

Labs (CBC with differential; serum chemistries, including glucose) will be performed as follows:
− *Dose escalation phase*: every week for the first cycle, then every 2 weeks for cycle 2 and then at the start of each cycle (up to 3 days before start of a new cycle) for the remainder of the study.
− *Expansion phase*: D1 and D8 of cycle 1, then at the start of each cycle (up to 3 days before start of a new cycle).

EKG will be performed as follows:
− *Dose escalation phase*: at baseline, on C1D1 (3-6 hours after the first dose of ARQ 197) and on C1D15 (3-6 hours after the morning dose of ARQ 197) and as clinically indicated.
− *Expansion phase*: at baseline, on C1D1 (3-6 hours after pazopanib), on C1D8 (3-6 hours after pazopanib), on C2D1 (3-6 hours after the morning dose of ARQ 197), and as clinically indicated.

Evaluation of urine protein/creatinine ratio will be performed as follows:
− *Dose escalation phase*: at baseline, on C1D15, then at the start of each cycle.

− *Expansion phase*: at baseline, on C1D8, then at the start of each cycle, and as clinically indicated.

Echocardiogram or MUGA scan for assessment of LV ejection fraction will be performed at baseline and as clinically indicated.

CT scans will be performed at baseline, and repeat imaging scans will be performed every 2 cycles.

As part of a risk mitigation plan for possible hepatic failure, serum liver tests (AST, ALT, serum bilirubin) will be monitored before initiation of treatment with pazopanib and at weeks 3, 5, 7, and 9. Thereafter, monitoring will occur at months 3 and 4, and as clinically indicated. Periodic monitoring will continue after month 4.

5.1 Agent Administration

5.1.1 Dose Escalation Phase

A primary objective of the trial is to establish the safety, tolerability, and MTD of the combination. Pazopanib will be administered QD, starting at 400 mg, and ARQ 197 will be administered BID, starting at 120 mg (dose level 1). The duration of a cycle will be 28 days (± 1 day for scheduling). Dose escalation will proceed in cohorts of 3 patients each (3+3 design) as outlined below (Table 2):

Table 2: Dose Escalation Scheme

Dose Level	Pazopanib	ARQ 197
-2	200 mg QD	120 mg QD
-1	400 mg QD	120 mg QD
1 (starting dose)	400 mg QD	120 mg BID
2	600 mg QD	120 mg BID
3	600 mg QD	240 mg BID
4	800 mg QD	240 mg BID
5	800 mg QD	360 mg BID
6*	600 mg QD	360 mg BID

*If dose level 5 is above the MTD, dose level 6 will be evaluated.

Tumor biopsies will be optional during the escalation phase. For the escalation phase, 3 patients should have completed at least one cycle of therapy prior to considering dose escalation in the next cohort of patients. Dose escalation will proceed according to the following scheme. DLT is defined in Section 5.2. Determination of DLT will be based on toxicities observed in the first cycle of therapy. Patients are considered evaluable for toxicity for the purpose of cohort dose escalation decisions if they either 1) experienced DLT or 2) have received at least 80% of the planned 28-day doses of treatment in one cycle of therapy and have been followed for one full cycle without DLT. All toxicities will be reported for all patients who receive any amount of study drug on this study. Evaluation of toxicity will begin with study drug administration on cycle 1 day 1.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended Phase II dose. At least 6 patients must be entered at the recommended Phase II dose.

5.1.2 Expansion Phase

Once the MTD is established, an additional cohort of patients will initially be treated with pazopanib alone, and tumor biopsies will be obtained to assess target inhibition, as outlined below. Tumor biopsies will be mandatory during the expansion phase of the study. Biopsies will be obtained at the time points outlined below. Depending on the results obtained from the tumor biopsies in the first few patients, the timing of the biopsy can be adjusted, but the number of tumor biopsies and the procedure will not change. Any change in the timing of the tumor biopsy will be discussed with the patient prior to obtaining informed consent.

The cohort and dosing regimens after establishment of the MTD are described below. When administered as a single agent during the expansion phase, the dose of pazopanib will correspond to the dose determined for the combination MTD if the MTD is determined at dose level 5 (ARQ 197 360 mg BID/pazopanib 800 mg QD) or 6 (ARQ 197 360 mg BID/pazopanib 600 mg QD). Otherwise, the dose of pazopanib will be determined after discussion with CTEP. Once the MTD is established, the data will be discussed with CTEP prior to proceeding with accrual for the expansion phase.

Cohort A (12 patients): Pazopanib will be given once daily as single agent from cycle 1 day 1 to day 7. Tumor biopsy will be done before drug administration on study (baseline) and on cycle 1 day 8, 8-12 hours after pazopanib administration. **After** the tumor biopsy, patients will start to receive ARQ 197 in addition to pazopanib at the combination MTD.

Twelve evaluable patients with both pre- and post-treatment biopsies will be treated initially in Cohort A. Mean increases in MET and pMET in these 12 patients will be measured to assess whether or not they are statistically significant.

For the purposes of final analysis of the expansion phase, only patients with paired tumor biopsies will be considered evaluable. Patients with fewer than the 2 required biopsies will not be considered evaluable for the expansion phase and will need to be replaced in the accrual scheme of the expansion phase. If a patient has a dose-limiting toxicity (DLT) with the single lead-in agent pazopanib in the expansion cohort, the patient will be taken off treatment.

5.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as an adverse event that is related (possibly, probably, or definitely) to administration of study drugs and fulfills one of the following criteria:

5.2.1 Grade ≥ 3 Non-Hematological Toxicity

Grade ≥ 3 non-hematological toxicity felt to be related to study medications will be considered dose-limiting with the following clarifications:

5.2.1.1 Diarrhea Grade 3 will only be considered dose-limiting if it is refractory to treatment as outlined in Section 5.3.2, Supportive Care Guidelines, and unable to be corrected to Grade 2 or less within 24 hours. Bloody or Grade 4 diarrhea will be dose-limiting.

5.2.1.2 Nausea and vomiting Grade 3 will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 24 hours (Section 5.3.1).

5.2.1.3 Rise in creatinine to Grade 3, not corrected to Grade 1 or less within 48 hours with IV fluids will be considered dose-limiting. All Grade 4 rises in creatinine will be dose limiting.

5.2.1.4 Grade ≥ 3 metabolic toxicities unable to be corrected to Grade 2 or less within 48 hours (such as glucose changes, hypocalcemia or hypercalcemia, hypomagnesemia or hypermagnesemia, hyperuricemia, hypophosphatemia, and hyponatremia) will be considered dose limiting. For hypokalemia or hyperkalemia, grade ≥ 2 toxicities unable to be corrected to grade 1 or less within 48 hours will be considered dose limiting. Grade 4 metabolic toxicities that are symptomatic will be considered dose-limiting regardless of duration or ability to correct.

5.2.1.5 QTc prolongation to ≥ 500 msec on at least two separate EKGs (refer to Section 5.3) will be dose limiting.

5.2.1.6 AST/ALT > 8 X ULN or AST/ALT > 3 X ULN and concurrent bilirubin elevation > 2 X ULN will be dose limiting.

5.2.1.7 Grade ≥ 3 bleeding in any sites or grade ≥ 2 pulmonary bleeding will be dose limiting.

5.2.1.8 Grade 4 venous thrombosis, pulmonary embolism, or any grade of arterial thrombosis will be dose limiting.

5.2.2 Grade 4 thrombocytopenia.

5.2.3 Grade 4 neutropenia ≥ 3 days or febrile neutropenia.

5.2.4 Any degree of anemia, leucopenia in the absence of grade 4 neutropenia ≥ 3 days, or lymphopenia will not be considered dose limiting.

5.3 General Concomitant Medication and Supportive Care Guidelines

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient. Particular attention must be paid to medications which may prolong the QTc interval (Appendix C) and agents that interact with CYP450 isoenzymes (Appendix B).

QTc Prolongation:
Caution should be exercised when administering pazopanib to patients with a history of QTc interval prolongation, in patients taking anti-arrhythmics or other medications that may prolong the QTc interval, and those with relevant pre-existing cardiac disease. A list of medications that may cause QTc interval prolongation are listed in Appendix C, and should be avoided by patients on this study. EKG will be performed as described in Section 5. If the QTc interval on follow-up EKG is ≥ 500 msec, the EKG should be repeated within 7 days and, if the QTc interval remains ≥ 500 msec, the subject should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at <500 msec, the EKG should be repeated within 7 days. If the repeat EKG again shows a ≥ 60 msec increase in the QTc interval from baseline, consideration should be given to removing

the subject from the study or increasing monitoring, after discussion with the principal investigator.

CYP450 Interactions:
In vitro and in vivo animal data indicate that the metabolism of pazopanib is primarily mediated by CYP3A4. In vitro data indicate that pazopanib is a potential inhibitor for CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In addition, one in vitro study suggested that pazopanib may induce CYP3A4 at high concentrations. Potent CYP3A4 inhibitors and inducers are prohibited on pazopanib trials. In exceptional circumstances, medications which strongly inhibit CYP3A4 may be administered, with caution, if the dose of pazopanib is decreased to 50% of the dose which would otherwise be administered.

Medications that strongly inhibit CYP3A4 include (but are not limited to):
- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antidepressant: nefazodone

Grapefruit juice is also an inhibitor of CYP450 and should not be taken with pazopanib.

Medications that strongly induce CYP3A4 include (but are not limited to):
- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Drugs that have narrow therapeutic windows and are substrates for these enzymes should be avoided and, if necessary, administered with caution (see Appendix B). Because of pazopanib's long half-life, caution should continue to be exercised for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications.

Medications that are substrates for these enzymes *and* have narrow therapeutic windows 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

In vitro studies indicate ARQ 197 is metabolized by CYP2C19, and to a lesser extent CYP3A4. The metabolism and consequently overall pharmacokinetics of ARQ 197 could be altered by inhibitors and/or inducers or other substrates of CYP2C19 and CYP3A4. In patients receiving any medications or substances that are inhibitors or inducers of CYP3A4 or CYP2C19, every attempt should be made to change the medications to another agent that does not affect the CYP pathway (see Appendix B).

Specific recommendations regarding other oral hypoglycemics:
Co-administration of pazopanib with some oral hypoglycemics, including glipizide, glyburide, (glibenclamide), glimerpiride, nateglinide, repaglinide, gliclazide, acetohexamide, carbutamide, glibornuride, glymidine, metahexamide, and tolazmide, (but not including tolbutamide and chlorpropamide, which are prohibited) may result in an increase in plasma concentrations of the oral hypoglycemic agents, leading to hypoglycemia. Therefore, reducing the doses of these oral hypoglycemic agents should be considered when pazopanib administration starts. The blood glucose should be monitored closely and patients should be instructed to measure their blood glucose if they experience symptoms of hypoglycemia and inform their physicians if their blood glucose concentrations are low. After at least 14 days of pazopanib administration, the doses of oral hypoglycemic agents may be increased **as necessary** to maintain adequate blood glucose control.

Specific recommendations regarding non-dihydropyridine calcium channel blockers:
Co-administration of pazopanib with calcium channel blockers may result in increased plasma concentrations of the latter. The 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 PR interval > 200 msec, sinus bradycardia (< 60 beats per minute), or second or third degree heart block, unless the patient has a permanent pacemaker.

5.3.1 Nausea/Vomiting

Anti-emetics will not be administered routinely prior to pazopanib or ARQ 197. However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT_3 antagonists, or aprepitant may be given. In addition, if a patient develops nausea and/or vomiting that is Grade 2 or greater, anti-emetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 with treatment with a combination of at least 2 of the antiemetics within 24 hours.

5.3.2 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours (4 mg every 4 hours while asleep), till resolution of episode of at least 12 hours (no more than 16 mg of loperamide

during a 24-hour period). This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours to ≤ Grade 2 with the above regimen (maximum of 16 mg of loperamide in a 24-hour period). If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated.

5.3.3 Neutropenia

To reduce the risk of severe myelosuppression events, a complete blood count (CBC) should be performed weekly during cycle 1, every 2 weeks during cycle 2, and at the start of each subsequent cycle (up to 3 days before start of new cycle) in the dose escalation phase. In the expansion phase, CBC will be performed on D1 and D8 of cycle 1, then at the start of each cycle (up to 3 days before start of new cycle). Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

5.3.4 Anemia

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org/).

5.3.5 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

5.3.6 Reflux/Gastritis

Antacids and other anti-ulcer medications such as histamine H2-receptor antagonists may be used if clinically indicated. To avoid significantly altering gastric pH, when needed, these medications should be used 4 hours after study drug administration. Proton pump inhibitors such as omeprazole and lansoprazole, which have a potential for interaction with ARQ 197, should be avoided.

5.4 Duration of Therapy

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

- Significant toxicity occurs despite 2 dose reductions as described in Section 6 or no lower dose level exists
- Pregnancy
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via biweekly phone calls.

5.6 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow-up period or toxicities are unresolved but stabilized. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated by fax to Central Registration per Section 4.

6 DOSING DELAYS/DOSE MODIFICATIONS

Toxicities (hematologic and non-hematologic; except any grade lymphopenia, anemia, or alopecia) should have resolved to ≤ Grade 2 prior to starting the next cycle or receiving the next dose of pazopanib or ARQ 197 within a cycle. Study drugs should be held for hypokalemia or hyperkalemia ≥ grade 2; hypocalcemia or hypercalcemia ≥ grade 3; hypophosphatemia ≥ grade 3; hypomagnesemia or hypermagnesemia ≥ grade 3. These laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment. Study drugs may be re-administered when hypokalemia or hyperkalemia is grade 1 or within institutional limits; hypocalcemia or hypercalcemia is ≤ grade 2; hypophosphatemia is ≤ grade 2; and hypomagnesemia or hypermagnesemia is ≤ grade 2. Even though study drug administration is allowed at these lower grades, every effort should be made to correct the abnormal lab values to normal if possible. If the potassium level is grade 2 or greater and/or if the calcium, magnesium, and/or phosphate are grade 3 or higher, an EKG must be performed and appropriate action taken based on the results.

Treatment may be delayed for a maximum of 2 weeks for toxicities. In case toxicities do not resolve as stated, the patient will not receive further therapy on this protocol and will be followed for resolution of toxicities. Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Dose modifications are intended for within-cycle and start-of-next-cycle changes. If administration of study drug is interrupted for any reason, it will not be made up, and

counting of the cycle days continues (i.e., if a patient stops pazopanib and ARQ 197 on day 15 and resumes 2 days later, they will be considered day 17).

A maximum of 2 dose reductions will be allowed before patient is taken off treatment. Patients who require a dose reduction will not have the dose re-escalated. Dose reductions may occur to a single compound independent of the other compound if toxicity necessitating a dose reduction is attributed to a single agent in the opinion of the study Principal Investigator. One dose level reduction due to pazopanib-associated toxicities such as hypertension means that pazopanib dose should be reduced to 400 mg if an original dose is 600 mg or to 600 mg if it is 800 mg. Similarly, one dose level reduction due to ARQ 197-associated toxicities means that ARQ 197 dose should be reduced to 120 mg bid if an original dose is 240 mg bid, or to 240 mg bid if it is 360 mg bid.

6.1 Dose Reduction

6.1.1 Doses will be modified for grade 3 or greater non-hematologic toxicity with the following clarifications:

- Doses will not be modified for electrolyte abnormalities, unless these are not correctable within 48 hours, or for alopecia.
- Dose of study drugs will not be reduced for nausea, vomiting, or diarrhea unless these are considered refractory as defined in Section 5.3.
- Dose reductions may occur to a single compound, independent of the other compound. Doses of ARQ 197 will not be reduced for any grade hypertension or proteinuria.
- For uncontrolled hypertension (as defined in Section 6.1.5), only the dose of pazopanib will be reduced to the next lower dose level.
- For proteinuria, only the dose of pazopanib will be reduced to the next lower dose level (Section 6.1.6).

6.1.2 Grade 2 drug-related toxicity: No changes will be made to the dose of either study drug for Grade 2 toxicities, and therapy will not be interrupted, except as otherwise noted (e.g., hypokalemia or hyperkalemia as described above, Grade 2 hemorrhage or thrombosis as described in Section 6.1.10). However, for persistent symptomatic skin rash or hand foot syndrome limiting instrumental activities of daily living that do not improve to grade 1 or less within 2 weeks with optimal management, doses of both pazopanib and ARQ 197 will be held until toxicities have resolved to ≤ Grade 1 prior to re-starting study treatment. Therapy will be re-initiated at the next lower dose level.

6.1.3 Grade 3 drug-related neutropenia and/or thrombocytopenia: Doses of both pazopanib and ARQ 197 will be held until toxicities have resolved to ≤ Grade 2 prior to re-starting study treatment. Therapy will be re-initiated at the same dose level at the first occurrence of either event. In the case of second occurrence of

either event, therapy will be re-initiated at the next lower dose level. Therapy will not be interrupted or doses modified for any grade lymphopenia, anemia, or leucopenia in the absence of grade 3 or 4 neutropenia.

6.1.4 Grade 4 drug-related neutropenia ≥3 days and/or thrombocytopenia: Doses of both pazopanib and ARQ 197 will be held until toxicities have resolved to ≤ Grade 2 prior to re-starting study treatment. Therapy will be re-initiated at the next lower dose level.

6.1.5 Hypertension toxicity

Therapeutic BP monitoring by a health care provider will occur every 2 weeks during the first 2 cycles then at least every cycle for the duration of treatment in the dose escalation phase, and on D1 and D8 of cycle 1 then at least every cycle in the expansion phase. All patients will be required to monitor their BP at least once a day (preferably BID) throughout the treatment and record the readings in the study diary (Appendix E). Table 3 will be used for the grading of pazopanib-associated hypertension, for immediate and long-term management, and for the determination of pazopanib dose modification. Suggested antihypertensive medications are listed in Table 4.

Table 3: Recommended Hypertension Monitoring and Management (BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No Change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99	Step 1) Initiate BP treatment and if needed, after 24-48 hr of treatment, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at maximum dose of medication Step 2) If BP still not controlled, add another anti-hypertensive medication, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of pazopanib or stopping pazopanib	BP should be monitored as recommended by the treating physician	No change except as described in step 4

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib Dose Modification
	NOTE: Stopping or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly		
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100	HOLD pazopanib until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic: optimal management with intensive IV support in ICU; STOP pazopanib and notify hospital staff that stopping pazopanib may result in a decrease in BP** **and** **2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, 2 new antihypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD pazopanib until systolic BP ≤159 and diastolic BP ≤99. After this, pazopanib may be re-administered. If BP is still grade 2, manage as described above for grade 2 hypertenison. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of pazopanib when systolic BP ≤159 and diastolic BP ≤99 or stopping pazopanib. **HOWEVER,** **If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue pazopanib or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib at 1 lower dose level after consultation with the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP pazopanib and notify hospital staff that stopping pazopanib may result in a decrease in BP**	Intensive	Permanently discontinue pazopanib or if systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib Dose Modification
• If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy • If subjects require >2 dose reductions, discontinue protocol therapy • Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib • 24-48 hours should elapse between modifications of antihypertensive therapy • Hypertension should be graded using CTCAE v4			

Notes:

- While patients are receiving treatment with pazopanib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
- Decisions to hold or decrease the pazopanib dose during treatment must be based on BP readings taken in the clinic by a medical professional.
- Based on prior clinical experience with pazopanib, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

Table 4: Oral Antihypertensive Medications: Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Receptor Blockers (ARBs)	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

6.1.6 Proteinuria toxicity

Evaluation of urine protein/creatinine ratio (UPC) should occur as follows:
− *Dose escalation phase*: at baseline, on C1D15, then at the start of each cycle
− *Expansion phase*: at baseline, on C1D8, then at the start of each cycle.
If, at any time, a subject has a urine protein/creatinine ratio greater than 1, a 24 hour urine collection must be performed. If a subject develops the nephrotic syndrome, treatment must be discontinued.
Although subjects with ≥1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as Table 5:

Table 5: Pazopanib Dose Modifications for Proteinuria Toxicity

UPC > 1and < 3	Obtain 24-hr urine protein and if <3 g, continue at current dose and monitor as clinically indicated
UPC ≥ 3 or 24-h urine protein ≥ 3 g	Step 1. Interrupt pazopanib. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC >3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2 Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and remove subject from study.
Nephrotic syndrome	Permanently discontinue pazopanib and remove subject from study

6.1.7 Cardiac Toxicity

1. Discontinue pazopanib in patients who develop symptomatic heart failure.
2. Modify the pazopanib dose using the table presented in Appendix F in patients who develop compromised symptomatic LVEF. The NCI developed the table in Appendix F using the NSABP-B31 and NCCTG9831 monitoring guidelines for adjuvant trastuzumab in patients with breast cancer. These studies enrolled populations considered most likely to be cured; thus, the investigators used the most stringent and conservative monitoring.
3. Discontinue ARQ 197 in patients who develop symptomatic bradycardia.

4. Patients with asymptomatic bradycardia will not have drug held or dose modified. Bradycardic patients with a heart rate ≤ 50 beats per minute should have an EKG done on day 1 of every cycle, or as clinically indicated.
5. QTc Prolongation, see Table 6.

Table 6: Management of QTc Prolongation

If EKG reveals an increase in the QTc to ≥500 msec or an increase in the QTc by at least 60 msec from baseline	Repeat EKG before re-administration of pazopanib and/or ARQ 197
If repeat EKG shows QTc interval is ≥500 msec	Remove subject from study
If on repeat EKG, QTc remains at least 60 msec longer than baseline but is less than 500 msec	Consider removing subject from study

6.1.8 Management of Subjects with Elevations in AST, ALT and/or Bilirubin

Table 7: Management of Liver Function Test Abnormality

AST, ALT and/or Bilirubin	
Isolated AST/ALT elevations between 3X ULN and 8X ULN	Continue pazopanib, but monitor weekly until AST/ALT returns to ≤ 2.5 or baseline
AST/ALT >8 X ULN	Hold pazopanib until AST/ALT returns to ≤ 2.5 X ULN or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then consider reintroducing pazopanib at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks **only after discussion with the PI and CTEP.** If AST/ALT elevations >3 X ULN recur, then pazopanib should be permanently discontinued.
AST/ALT >3 X ULN and concurrent bilirubin elevations >2 X ULN	Permanently discontinue pazopanib.
Mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 X ULN	Continue pazopanib, but monitor weekly until ALT returns to grade 1 (NCI CTCAE) or baseline.

6.1.9 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome

RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with pazopanib therapy (<3%). Clinical presentations are variable and may include altered mental status, seizure, and cortical visual deficit.

Hypertension is a common risk factor in patients who develop RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the

gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status changes, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage. Pazopanib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Pazopanib should be discontinued upon diagnosis of RPLS.

After consultation with the study PI and CTEP, NCI, consideration of restarting the study drugs may be evaluated in light of any clinical benefit.

6.1.10 Management of Other Adverse Events

Adverse Event	Grade	Treatment Modification
Hemorrhage/ Bleeding	Grade 1	No interruption in treatment until hemoptysis. If hemoptysis, contact PI to determine if it is appropriate to continue pazopanib. Maintain current dose.
	Grade 2	For non-pulmonary bleeding, hold pazopanib unless resolved to ≤ grade 1; reduce dose to next lower dose level, and continue treatment. For pulmonary bleeding, permanently discontinue pazopanib and remove subject from study. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop pazopanib and remove subject from study.
	Grades 3 or 4	Discontinue treatment and withdraw subject from study.
Vascular/ Thrombosis	Grade 1	No interruption in treatment; maintain current dose.
	Grade 2, 3	Hold pazopanib until subject is receiving a stable dose of Low Molecular Weight Heparin (LMWH). Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have been treated with an anticoagulant at the desired level for at least one week. • The subject must not have had a grade 3 or 4 or significant grade 2 hemorrhagic event while on anticoagulant. 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 dosing (e.g., re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
	Grade 4 or pulmonary embolus	Discontinue treatment and remove subject from study.
Arterial Thrombosis/ ischemia	All grades	Discontinue pazopanib and remove subject from study.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following lists of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1 CAEPR for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for Pazopanib (GW786034)

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6[1], January 21, 2015

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 2)***

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 3)***
	Headache		***Headache (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[6]		***Respiratory hemorrhage[6] (Gr 2)***
		Respiratory, thoracic and mediastinal disorders – Other (interstitial lung disease)[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation)			***Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[8]	
		Vascular disorders - Other (arterial thromboembolic event)[8]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[6]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[7]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

[8]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

[9]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events also reported on Pazopanib (GW786034) trials but with the relationship to Pazopanib (GW786034) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Cardiac disorders - Other (Torsades de Pointes); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia

ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders – Other (eye/retinal hemorrhage); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INFECTIONS AND INFESTATIONS - Infection[9]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; GGT increased; INR increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

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

7.1.2 CAEPR for ARQ 197 (NSC 750832)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf* for

further clarification. Frequency is provided based on 579 patients. Below is the CAEPR for ARQ 197 (tivantinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, June 17, 2013[1]

Adverse Events with Possible Relationship to ARQ 197 (tivantinib) (CTCAE 4.0 Term) [n= 579]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
	Sinus bradycardia		
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
INVESTIGATIONS			
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on ARQ 197 (tivantinib) trials but with the relationship to ARQ 197 (tivantinib) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Lymph node pain
CARDIAC DISORDERS - Cardiac arrest
EYE DISORDERS - Dry eye; Eye disorders - Other (blindness unilateral)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Constipation; Dry mouth; Duodenal ulcer; Dyspepsia; Flatulence; Gastrointestinal disorders -

Other (eructation [belching]); Gastrointestinal disorders - Other (peritoneal hemorrhage); Mucositis oral; Oral pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Gait disturbance; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis; Hepatic failure
Infections and infestations – Infection[2]
Injury, poisoning and procedural complications - Fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (pancytopenia); Platelet count decreased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain; Pain in extremity
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (hydronephrosis); Urinary retention; Urinary tract obstruction
Reproductive system and breast disorders - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Bronchospasm; Cough; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin hyperpigmentation
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: ARQ 197 (tivantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

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

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1).

- **Attribution** of the AE:
  1. Definite – The AE *is clearly related* to the study treatment.
  2. Probable – The AE *is likely related* to the study treatment.
  3. Possible – The AE *may be related* to the study treatment.
  4. Unlikely – The AE *is doubtfully related* to the study treatment.
  5. Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.2).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted] Once Internet connectivity is restored, the 24-hour notification phoned in **MUST** be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., CTEP-AERS). These are: any grade lymphopenia, grade 2 hypophosphatemia, grade 2 hyperglycemia, any grade alopecia, grade 2 anemia, grade 2 electrolytes (sodium, potassium, and magnesium), grade 2 albumin, grade 2 INR, grade 2 PTT, and grade 2 hyperuricemia will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.3.4 Pregnancy, Fetal Death, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or
"Neonatal loss", the Pregnancy Information Form should be completed and faxed along with any additional medical information to [redacted]. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

7.3.4.1 Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure

of the fetus to agents which may be teratogenic. For this reason, pregnancy should be reported in an expedited manner via CTEP-AERS as Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*" under the *Pregnancy, puerperium and perinatal conditions* SOC.

- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

7.3.4.2 Fetal Death

- Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."
- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.
- A fetal death should NOT be reported as "Fetal death," a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.3.4.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration - Other (neonatal loss)" under the General disorders and administration SOC.
- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.3.4 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

7.3.4.1 Definitions

Adverse Event
An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or

clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

Suspected adverse reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse reaction
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious
An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

Serious Adverse Events
An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Disability
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience
Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB approved research protocol.

Non-compliance (NIH Definition)
The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.4.2 Requirements

The NCI-IRB **requires** that the following language be used for reporting events to the NCI-IRB:

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.3.4.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.4.1 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

For reporting of adverse events at time of continuing review, the NCI-IRB requires a summary report of adverse events that have occurred on the protocol **since the previous continuing review and in aggregate**. The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk: benefit determination. Please sort the events by the system organ class and by grade. The summary report is based on the following guidance: any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.

Please use the following table for reporting adverse events at time of CR:

System Organ Class	CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

8.1 Pazopanib (GW786034) (NSC 737754)

Chemical Name:	5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride
Other Names:	Pazopanib HCl, GW786034B (the suffix B denotes the monohydrochloride salt)
Classification:	VEGFR tyrosine kinase inhibitor
Molecular Formula:	$C_{21}H_{23}N_7O_2S \bullet HCl$
Molecular Weight:	474.0 g/mol (monohydrochloride salt)

	437.5 g/mol (free base)
Physical Form:	White to slightly colored solid
Solubility:	Very slightly soluble in 0.1M HCl (0.65 mg/mL); practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL) and in pH 11 piperidine buffer (0.0002 mg/mL).
Mode of Action:	Pazopanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.
How Supplied:	Pazopanib monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200 mg and 400 mg of the free base: • 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each • 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each Tablet excipients in all tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, polyethylene glycol, and polysorbate 80.
Storage:	The intact bottles should be stored at controlled room temperature [20°C-25°C, (68-77°F)]. Excursions are permitted between 15°C and 30°C.
Stability:	Stability studies are ongoing.
Route of Administration:	Oral pazopanib should be taken on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be swallowed whole and cannot be crushed or broken.
Potential Drug Interaction:	See Section 5.3.
Availability	Pazopanib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Pazopanib is provided to the NCI under a Collaborative Agreement between GlaxoSmithKline and the DCTD, NCI (see Section 12.3).

8.2 ARQ 197 (NSC 750832)

Chemical Name:	(-)-*trans*-3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione
Other Names:	Tivantinib
CAS Registry Number	905854-02-06
Classification:	c-MET inhibitor

Molecular Formula:	$C_{23}H_{19}N_3O_2$
Molecular Weight:	369.43
Solubility:	Soluble in DMSO
Mode of Action:	c-MET inhibitor ARQ 197 binds to the c-MET protein and disrupts c-MET signal transduction pathways, which may induce apoptosis in tumor cells overexpressing c-MET protein or expressing constitutively activated c-MET protein.
Description:	Off-white to light to dark orange powder.
How Supplied:	ArQule supplies and CTEP's Pharmaceutical Management Branch distributes ARQ 197 in 120 mg tablets in 50 mL high-density polyethylene bottles with polypropylene caps. ARQ 197 tablets are red orange film coated and round with a diameter of 9.2 mm. Inert ingredients include lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, purified water, and magnesium stearate. The film coating contains purified water, hypromellose, titanium dioxide, talc and ferric oxide. Each bottle contains 100 tablets.
Storage:	Store at controlled room temperature (20-25ºC) with excursions allowable to 15-30ºC.
Stability:	Stability studies of the intact bottles are ongoing.
Route*(s)* of Administration:	Oral
Method of Administration:	ARQ 197 tablets should be administered twice daily approximately 12 hours apart. They should be taken with water, swallowed whole and cannot be crushed or broken. ARQ 197 should be taken with food.
Potential Drug Interaction:	ARQ 197 is metabolized via a drug metabolizing enzyme system associated with cytochrome P450 (CYP2C19 and CYP3A4). Interactions with drugs metabolized via the same enzyme system are possible. Drugs which inhibit CYP2C19 may markedly increase the plasma concentration of ARQ 197. Drugs and substances which inhibit CYP3A4 may increase the plasma concentrations of ARQ 197. (Refer to http://medicine.iupui.edu/flockhart/table.htm)
Availability:	ARQ 197 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. ARQ 197 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.3 Agent Ordering

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call [redacted]. Monday through Friday between 8:30 am and 4:30 pm (ET) or e-mail [redacted] anytime.

8.4 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP Web site at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

With Amendment H, dated 09/26/2013: For patient convenience, 2 months' worth of drug may be dispensed at a time to patients who have been on study for 6 cycles or more and who are tolerating treatment well.

9 CORRELATIVE/SPECIAL STUDIES

9.1 Pharmacodynamics

9.1.1 Laboratory Contact

At least 24 hours prior to biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail [redacted]. For biopsies, tubes pre-labeled with the information specified in Section 9.1.4,

biopsy date, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

9.1.2 Tumor Biopsies

9.1.2.1 Timing of tumor biopsies

Biopsies will be collected optionally during the escalation phase:

- before drug administration on study (baseline), and
- on cycle 1 day 8; 8-12 hours after the Day 7 evening dose of ARQ 197 (the morning dose of ARQ 197 will be taken 1 hour after pazopanib)

Biopsies will be mandatory during the expansion phase:
Cohort A

- before drug administration on study (baseline), and
- on cycle 1 day 8, 8-12 hours after pazopanib and before the first dose of ARQ 197

The C1D8 biopsy can be collected on C1D7 for scheduling reasons.
Tumor biopsy requires fasting during at least 8 hours after food taken with ARQ 197.

9.1.2.2 Biopsy Procedure

Serial tumor biopsies will be obtained through Interventional Radiology by a percutaneous approach. A maximum of 2 core biopsies 18-gauge in diameter and at least 1 cm in length will be obtained at each time point. Only percutaneous biopsies will be performed on patients with solid tumors.

It is estimated that there will be between 2-5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made. Determination of a disease site amenable to biopsy will be determined on an individual case basis after discussion with an interventional radiologist. The biopsy procedure to be used in this protocol is described below; local anesthesia will be administered. Such biopsies can be safely performed as evidenced by literature reports [31] as well as our experience at the Clinical Center. Risks of the procedure include, but are not limited to, bleeding, infection, pain, and scarring. We will follow Clinical Center Interventional Radiology SOPs for coagulant panel and platelets.

- All biopsies will be by percutaneous approach
- No biopsy by an invasive (endoscopic, laparoscopic, or surgical) procedure will be performed.
- Only cutaneous, subcutaneous, or easily accessible parenchymal lesion core biopsies will be performed.

- However, there will be no core biopsies of lung lesions. Only fine needle aspiration (FNA) of a lung lesion may be performed at the discretion of the PI after discussion with an interventional radiologist.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. All cases will be carefully reviewed with the interventional radiologists at NIH who have extensive experience in performing such procedures. Only if the procedure is considered to be low risk will we proceed with tumor biopsy in a given participant.

Disease amenable to biopsy and willingness to undergo tumor biopsies is required for patients to enroll in the expansion phase. Tumor biopsy is optional in the escalation phase. Baseline biopsies will be performed following patient enrolling on study for Cohort A only. If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed. However, for the purposes of final analysis of the expansion phase of Cohort A, only patients with paired tumor biopsies will be considered evaluable. Patients with fewer than the 2 required biopsies will not be considered evaluable for the expansion phase and will need to be replaced in the accrual scheme of the expansion phase.

9.1.2.3 Solid Tumor Biopsy Processing

Two tissue cores will be collected. One sample will be immediately flash frozen in liquid nitrogen for alternate determination of MET PD biomarkers. The second core will be immediately flash frozen in liquid nitrogen for determination of HIF-1α, pathology, MET gene sequencing, and epithelial-mesenchymal transition (EMT) marker analysis. The frozen biopsy specimens are transferred to PADIS, where the core biopsy sample is stored at -80°C. Biopsy samples will be analyzed for total MET, p-MET, HIF-1α, and EMT markers such as e-cadherin, beta catenin. Sequencing for known mutations in the kinase and ligand binding domains will be performed in tumor biopsies.

Biopsies for PD analysis will be shipped on dry ice to Dr. Kinders' laboratory for analysis:

[redacted]

[redacted]

9.1.3 Blood Samples

Assays to be performed: sMET, HGF, VEGF-A, and sVEGFR2. These research blood tests are mandatory and will be required for every patient.

Samples will be obtained at the following time points:

Dose Escalation Phase

- before drug administration on study (baseline)
- C1D1: 2, 4, and 6 hours after pazopanib
- C1D15, before drug administration
- C2D1, before drug administration

Expansion Phase

- before drug administration on study (baseline)
- C1D1: 2, 4, and 6 hours after pazopanib
- C1D8, before drug administration
- C2D1, before drug administration

Blood samples should be obtained using EDTA as an anticoagulant (lavender top tubes); the minimum volume of blood needed for analysis of all four markers is 3 mL.

Plasma should be prepared from the blood samples within 1 hour (with interim storage and handling at 4ºC); plasma should be transferred to new screw cap cryovial (silicon gasket), pre-labeled with bar code.

Samples should be shipped to:

[redacted]

9.1.4 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., urine, blood, tumor biopsy, skin punch biopsy,

circulating tumor cells, hair follicles, per specific protocol) will be recorded on a PK/PD collection worksheet included in Appendix H.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
100 series: urine for PK
200 series: blood for PK
300 series: blood for PD
400 series: blood for circulating tumor cells (CTCs)
500 series: tumor biopsies
600 series: skin punch biopsies
700 series: hair follicles
800 series: blood for pharmacogenomic analysis

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed

due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.2 Pharmacokinetics

9.2.1 Blood Sample Collection

9.2.1.1 Dose Escalation Phase

Blood samples for PK analysis will be collected prior to drug administration and at multiple time points after drug administration beginning on D1 and D15 of cycle 1 only. Pazopanib will be taken on an empty stomach 1 hour before a meal and ARQ 197 will be taken with food.

D1: pre-dose, and 1, 2, 4, 6, and 12 hours after administration of pazopanib, with the morning dose of ARQ 197 administered 1 hour after pazopanib and the evening dose of ARQ 197 administered after the 12-hour time point (corresponding to 1, 3, 5, and 11 hours after administration of ARQ 197). The actual time of collection will be noted for each sample.

D15: pre-dose, and 1, 2, 4, and 6 hours after administration of pazopanib, with the morning dose of ARQ 197 administered 1 hour after pazopanib (corresponding to 1, 3, and 5 hours after administration of ARQ 197). The actual time of collection will be noted for each sample.

9.2.1.2 Expansion Phase

Blood samples for PK analysis will be collected prior to drug administration and at multiple time points after drug administration beginning on D1 and D7 of cycle 1 only. Pazopanib will be taken on an empty stomach 1 hour before a meal and ARQ 197 will be taken with food.

Cohort A:
D1: pre-dose, and 1, 2, 4, 6, and 12 hours after administration of pazopanib.
D7: pre-dose, and 1, 2, 4, and 6 hours after administration of pazopanib.

The PK studies are mandatory and will be required for every patient. The total volume of blood collected for PK studies during the initial treatment cycle is expected to be < 70 mL per patient. Based on results from initial measurements, sampling times may be adjusted, but neither the total number of samples nor the total amount of blood drawn per patient will be increased. Samples will be collected in lavender-top (EDTA) tubes with 6 mL (3 mL for day 1 in Cohort A of the expansion phase) of blood per sample. It is important to fill the Vacutainer tubes to the specified collection volume. The tube containing blood for plasma preparation will be gently inverted 10 times to ensure

thorough mixing of anticoagulant and blood, then placed in a cool box containing crushed ice and/or water.

9.2.2 Blood Sample Preparation

All samples will be centrifuged within 45 min of collection, at 1,500 x g for 10 min at 4°C. Immediately following centrifugation, the separated plasma for each sample will be divided into three aliquots at the following volume:
1. Aliquot #1 (for pazopanib assay): 1.0 mL
2. Aliquot #2 (for ARQ 197 assay): 0.5 mL
3. Aliquot #3 (Back up sample): Remaining volume

Note: For samples from day 1 in Cohort A of the expansion phase, Aliquot #1 will be taken for analysis of single agent pazopanib.

Aliquot #1 of plasma should be transferred with a plastic pipette into a 1.8 mL Nunc Cryovial tube (provided by GlaxoSmithKline), and Aliquots #2 and #3 should be each pipetted into polypropylene cryogenic sample storage vials (with screw-cap) (provided by Daiichi Sankyo Pharma Development, Department of Drug Metabolism and Pharmacokinetics [DMPK]), designated Set 1 and Set 2. Then, they should be maintained being chilled before being transferred to freezer. Within 90 min after blood draw, the sample storage vials will be stored, still in upright position, in a -70°C freezer. PPD and Covance Inc., respectively will analyze the parent drug molecules and possibly metabolites of pazopanib and ARQ 197 in plasma. These facilities have extensive experience in the measurement of drugs and metabolites in body fluids.

9.2.3 Shipment of Samples

Specimens will be labeled with the following information:
Sample type, ID number (CTEP protocol number + unique patient accession number + 3-digit sample number), and collection time. The shipment must contain a complete sample manifest (electronic or paper) containing the sample type, ID number (CTEP protocol number + unique patient accession number + 3-digit sample number), and collection time, along with the name and address, including the telephone and fax numbers of the person responsible for sending the samples. No personally identifiable information will be sent with samples.

A phone call or fax communication should precede all sample shipments. A phone or fax communication must precede all HIV positive or other known infections sample shipments. Detailed sample inventory information must accompany the samples. Lack of paperwork or illegible information will delay sample login and project initiation. Samples that are unclearly or incompletely labeled may be subject to additional handling fees. PPD encourages submission of sample inventory information in electronic form.

Plasma samples will be shipped on dry ice via prepaid overnight mail (e.g., UPS or FedEx), Monday through Wednesday (please ensure that wherever possible samples are transported so as to arrive between the hours of 09:00 and 16:00):

PPD for pazopanib

[redacted]

Covance Inc. for ARQ 197

[redacted]

9.3 Pharmacogenetics (PG)

As emerging information regarding the safety and efficacy of ARQ 197 may become available in the future, samples will be retained for possible future research if the patient gives permission. The sample will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample in accordance with laboratory procedures. During this time, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time as long as there is DNA remaining. The PG test for CYP2C19 is mandatory and will be required for every patient.

9.3.1 Blood Sample Collection

As part of this study, a blood sample (1 x 10 mL) will be taken at baseline to evaluate the CYP2C19 genotype of subjects. Samples will be collected into a 10 mL EDTA polypropylene (lavender-top) blood collection tube. It is very important to collect a full tube. The sample should be stored at -70 °C until shipment.

9.3.2 Shipment of Samples

Samples will be shipped on dry ice at a regular interval to:

Covance Inc.

[redacted]

[redacted]

10 STUDY CALENDAR

Baseline history and physical exam are to be conducted within 72 hours prior to start of protocol therapy; laboratory evaluations (including serum liver tests) and EKG must also be done within 72 hours. Scans, x-rays, and echocardiogram or MUGA scan must be done ≤ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The duration of a cycle will be 28 days (± 1 day for scheduling). Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle.

10.1 Dose Escalation Phase

	Pre-Study	C1 W1 (D1-7)	C1 W2 (D8-14)	C1 W3 (D15-21)	C1 W4 (D22-28)	C2 W1 (D1-7)	C2 W2 (D8-14)	C2 W3 (D15-21)	C2 W4 (D22-28)	C3 W1 on	Off Treatment
Pazopanib[a]		X	X	X	X	X	X	X	X	X	
ARQ 197[a]		X	X	X	X	X	X	X	X	X	
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam[b]	X			X		X				X	X
Vital signs[c]	X			X		X		X		X	X
Height	X										
Weight	X					X				X	X
Performance status	X					X				X	X
CBC w/diff, plts[d]	X		X	X	X	X		X		X	X
Serum chemistry[d]	X		X	X	X	X		X		X	X
Coagulation	X										
Urine protein/creatinine ratio or 24-hour urine protein[e]	X			X		X				X	X
EKG[f]	X			X							
Echocardiogram/MUGA	X										
Adverse event evaluation		X----------X									X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.									X
B-HCG[g]	X										
Tumor biopsies[h]	X		X								
PD blood sampling[i]	X	X		X		X					
PG blood sampling[j]	X										
PK blood sampling[k]	X	X		X							

a: Pazopanib once daily (empty stomach) and ARQ 197 twice daily (with meals) at the assigned dose.

b: Physical examination at Clinical Center should be performed on day 1 and day 15, and then at the start of each cycle (up to 3 days before start of new cycle). For patients who have been on study for 6 or more cycles and are tolerating treatment well, physical exams may be performed once every 2 cycles (every 2 months).

c: BP monitoring by a health care provider should be performed every 2 weeks during the first 2 cycles and then at the beginning of subsequent cycles. For patients who have been on study for 6 or more cycles and are tolerating treatment well, BP monitoring may be performed once every 2 cycles (every 2 months). Mid-cycle BP check can be performed by any health care professional. Patients should measure and record their blood pressure at home at least once per day for the duration of the study.

d: Serum chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, magnesium, potassium, total protein, SGOT [AST], SGPT [ALT], sodium) and CBC w/diff, platelets should be performed within 72 hours of enrollment (pre-study) and weekly during cycle 1 (D8, D15 and D22 ± 1 day for scheduling conflicts), every 2 weeks during cycle 2 (± 1 day for scheduling

conflicts), and at the start of each cycle (up to 3 days before start of new cycle). For patients who have been on study for 6 or more cycles and are tolerating treatment well, lab tests may be performed once every 2 cycles (every 2 months). Serum liver tests (AST, ALT, serum bilirubin) will also be performed during weeks 3, 5, 7, and 9; thereafter, monitoring will occur at months 3 and 4, and as clinically indicated. Periodic monitoring will continue after month 4.

e: Evaluation of urine protein/creatinine ratio should occur at baseline (within 72 hours of enrollment), on C1D15 (± 1 day for scheduling conflicts), then at the start of each cycle, and as clinically indicated. If patient has urine protein/creatinine ratio >1+, obtain a 24 hour urine for protein and creatinine clearance.

f: EKG will be performed at baseline, on C1D1 (3-6 hours after the first dose of ARQ 197) and on C1D15 (3-6 hours after the morning dose of ARQ 197) and as clinically indicated.

g: Serum or urine pregnancy test (women of childbearing potential) within 1 week prior to enrollment.

h: Tumor biopsies are optional in the escalation phase: at baseline and on C1D8, 8-12 hours after the Day 7 evening dose of ARQ 197 (taken 1 hour after pazopanib).

i: Samples will be obtained at the following time points: at baseline, on C1D1 2, 4, and 6 hours after pazopanib), on C1D15 (pre-drugs), and on C2D1 (pre-drugs).

j: A sample for PG study will be obtained at baseline.

k: Blood samples for PK will be collected from all patients during cycle 1 only:
D1: pre-dose, and 1, 2, 4, 6, and 12 hours after administration of pazopanib. D15: pre-dose, and 1, 2, 4, and 6 hours after administration of pazopanib.

10.2 Expansion Phase

	Pre-Study	C1 W1 (D1-7)	C1 W2 (D8-14)	C1 W3 (D15-21)	C1 W4 (D22-28)	C2 W1 (D1-7)	C2 W2 (D8-14)	C2 W3 (D15-21)	C2 W4 (D22-28)	C3 W1 on	Off Treatment
Pazopanib[a]		X	X	X	X	X	X	X	X	X	
ARQ 197[a]		X	X	X	X	X	X	X	X	X	
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam[b]	X		X			X				X	X
Vital signs[c]	X		X			X				X	X
Height	X										
Weight	X					X				X	X
Performance status	X					X				X	X
CBC w/diff, plts[d]	X			X		X				X	X
Serum chemistry[d]	X		X	X		X		X*		X	X
Coagulation	X										
Urine protein/creatinine ratio or 24-hour urine protein[e]	X		X			X				X	X
EKG[f]	X		X			X*					
Echocardiogram/MUGA	X										
Adverse event evaluation		X----------X									X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.									X
B-HCG[g]	X										
Tumor biopsies[h]	X		X								
PD blood sampling[i]	X	X	X			X					
PG blood sampling[j]	X										
PK blood sampling[k]	X	X									

a: Pazopanib once daily (empty stomach) and ARQ 197 twice daily (with meals) at MTD dose. Single-agent pazopanib from C1D1 to D7 then the combination of ARQ 197 and pazopanib from C1D8 in Cohort A

b: Physical examination at Clinical Center should be performed on D1 and D8 and then at the start of each cycle (up to 3 days before start of new cycle). For patients who have been on study for 6 or more cycles and are tolerating treatment well, physical exams may be performed once every 2 cycles (every 2 months).

c: BP monitoring by a health care provider should be performed on D1 and D8 of cycle 1 and then at the beginning of subsequent cycles. For patients who have been on study for 6 or more cycles and are tolerating treatment well, BP monitoring may be performed once every 2 cycles (every 2 months). Patients should measure and record their blood pressure at home at least once per day for the duration of the study.

d: Serum chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, magnesium, potassium, total protein, SGOT [AST], SGPT [ALT], sodium) and CBC w/diff, platelets should be performed within 72 hours of enrollment (pre-study) and again on D18 of cycle 1, and

at the start of each cycle (± 1 day for scheduling conflicts). For patients who have been on study for 6 or more cycles and are tolerating treatment well, lab tests may be performed once every 2 cycles (every 2 months). Serum liver tests (AST, ALT, serum bilirubin) will also be performed during weeks 3, 5, 7 (*can be collected by patients' local physician), and 9; thereafter, monitoring will occur at months 3 and 4, and as clinically indicated. Periodic monitoring will continue after month 4.

e: Evaluation of urine protein/creatinine ratio should occur at baseline, on C1D8, then at the start of each cycle (± 1 day for scheduling conflicts), and as clinically indicated. If patient has urine protein/creatinine ratio >1+, obtain a 24 hour urine for protein and creatinine clearance.

f: EKG will be performed at baseline, on C1D1 (3-6 hours after the morning dose of pazopanib), on C1D8 (3-6 hours after pazopanib), on *C2D1 (3-6 hours after the morning dose of ARQ 197), and as clinically indicated.

g: Serum or urine pregnancy test (women of childbearing potential) within 1 week prior to enrollment.

h: Tumor biopsies are mandatory in the expansion phase: at baseline and on C1D8, 8-12 hours after pazopanib before the first dose of ARQ 197.

i: Samples will be obtained at the following time points: at baseline, on C1D1 (2, 4, and 6 hours after pazopanib), on C1D8 (pre-drugs), and on C2D1 (pre-drugs).

j: A sample for the PG study will be obtained at baseline.

k: Blood samples for PK will be collected from all patients during cycle 1 only on D1 and D7 as specified in Section 9.2.1.2.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 2 cycles. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study agents.

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

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.2 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the

study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.3 Response Criteria

11.3.1 Evaluation of Target Lesions

Response and progression will be evaluated using RECIST version 1.1. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria per Section 11.1.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, which is based on the long axis for non-nodal lesions and the short axis for nodal lesions of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, which is based on the long axis for non-nodal lesions and the short axis for nodal lesions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The

patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.4 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive 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, including the baseline measurements.

11.5 Confirmatory Measurement

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry for a minimum interval of 8 weeks.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

Data will be collected in the Center for Cancer Research C3D database. This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.1.2 Responsibility for Data Submission

N/A

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer

Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

12.3.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

12.3.2 For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

12.3.3 Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

12.3.4 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

12.3.5 Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

12.3.6 Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

E-mail: [redacted]

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

A primary objective of the trial is to establish the safety, tolerability, and MTD of the combination. Another primary objective is to evaluate changes in MET and phospho-MET following treatment with pazopanib and ARQ 197.

Twelve patients will be treated initially in Cohort A. Mean increases in MET and pMET in these 12 patients will be measured to assess whether or not it is statistically significant.

13.2 Sample Size/Accrual Rate

The study is designed to have 5 dose escalation cohorts, with a standard design using 3 patients per cohort, unless DLT is noted, in which case up to 6 patients may be enrolled in a cohort. With 6 dose levels, up to 36 patients may be enrolled for determination of the MTD. In addition, to

characterizing the pharmacodynamics of the combination, up to an additional 12 patients will be enrolled in the expansion phase, for a total of 54 patients. Only patients with paired tumor biopsies will be considered evaluable in the expansion phase. To allow for a few patients who may not be evaluable, the accrual ceiling will be set at 56 patients.

It is anticipated that 2-3 patients per month may be enrolled onto this trial. Thus, depending on the number of patients needed to reach the MTD, it is expected that 18 to 27 months will be required to accrue the number of patients necessary to complete the trial.

13.3 Analysis of Secondary Endpoints

We will assess pMET (1235/1356) reduction, MET reduction, VEGF reduction, TSP-1 increase, HIF1α increase, and change in EMT markers, descriptively (magnitude of change, with 2-sided 90% CI), in blood and tumor assays (where paired samples are available), for the various dose combinations in the escalation and expansion phases.

13.4 Reporting and Exclusions

13.4.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with study agents.

13.4.2 Evaluation of response – All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Justification for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of pazopanib and ARQ 197 on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that pazopanib and/or ARQ 197 may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to pazopanib and/or ARQ 197. HIV-positive patients on combination antiretroviral therapy are excluded from the study because of possible PK interactions with pazopanib and/or ARQ 197.

14.1.1 Participation of Children

This study includes patients 18 years of age and older. Because insufficient dosing or adverse event data are currently available on the use of pazopanib and ARQ 197 in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials. Studies will be performed in patients <18 years of age when it is appropriate to do so.

14.2 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Sections 5 and 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.3 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be

answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

14.4 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

The research component of this study required to obtain 2 CT tumor biopsies confers radiation exposure at an effective dose of 0.29 rem. This dose is below NIH RSC guidelines and represents a slightly greater than minimal risk to patients.

14.5 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at [redacted], on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: POTENTIAL DRUG INTERACTIONS

CYP2C19 Inhibitors

Amiodarone	Felbamate	Methoxsalen	Ritonavir
Amitriptyline	Fenofibrate	Methsuximide	Rosiglitazone
Amprenavir	Fluconazole	Miconazole	Saquinavir
Aprepitant	Fluoxetine	Moclobemide	Selegiline
Azelastine	Fluvoxamine	Modafinil	Sertraline
Bortezomib	Fosamprenavir	Nelfinavir	Sildenafil
Buprenorphine	Gefitinib	Nicardipine	Sulconazole
Cholecalciferol/Vitamin D_3	Gemfibrozil	Nilutamide	Telmisartan
Cimetidine	Imipramine	Olanzapine	Ticlopidine
Citalopram	Indinavir	Omeprazole	Tioconazole
Clotrimazole	Indomethacin	Orphenadrine	Topiramate
Clozapine	Isoniazid	Oxcarbazepine	Torsemide
Delavirdine	Ketoconazole	Paroxetine	Tranylcypromine
Diazepam	Lansoprazole	Pentamidine	Valdecoxib
Dimethyl sulfoxide	Letrozole	Pimozide	Valproic acid
Drospirenone	Loratadine	Pioglitazone	Voriconazole
Efavirenz	Losartan	Probenecid	Warfarin
Entacapone	Mephobarbital	Progesterone	Zafirlukast
Ethinyl estradiol	Mestranol	Propofol	
Ethotoin	Methimazole	Rabeprazole	

CYP2C19 Inducers

Aminoglutethimide	Fosphenytoin	Rifampin	St. John's wort (1)
Carbamazepine	Phenytoin		

CYP2C19 Substrates

Carisoprodol	Escitalopram	Methsuximide	Phenobarbital
Cilostazol	Esomeprazole	Moclobemide	Phenytoin
Citalopram	Fosphenytoin	Nelfinavir	Progesterone
Clobazam	Imipramine	Nilutamide	Rabeprazole
Clomipramine	Lansoprazole	Omeprazole	Sertraline
Desogestrel	Mephenytoin	Pantoprazole	Trimipramine
Diazepam	Mephobarbital	Pentamidine	Voriconazole

When ARQ 197 is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of ARQ 197 is the potential outcome. The co-administration of 'inducers' would potentially lower plasma ARQ 197 concentrations. When drugs classified as 'substrates' are co-administered with ARQ 197, there is the potential for higher concentrations of the 'substrate'.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

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CYP3A4 Inhibitors

Acetaminophen	Cyclosporine	Glyburide	Modafinil	Ranolazine
Acetazolamide	Danazol	Grapefruit juice (2)	Nefazodone	Risperidone
Amiodarone	Dasatinib (1)	Haloperidol	Nelfinavir	Ritonavir
Amlodipine	Delavirdine	Hydralazine	Nevirapine	Saquinavir
Amprenavir	Desipramine	Ifosfamide	Nicardipine	Selegiline
Anastrozole	Dexmedetomidine	Imatinib	Nifedipine	Sertraline
Aprepitant	Diazepam	Indinavir	Nisoldipine	Sildenafil
Atazanavir	Diclofenac	Irbesartan	Nizatidine	Sirolimus
Atorvastatin	Dihydroergotamine	Isoniazid	Norfloxacin	Sulconazole
Azelastine	Diltiazem	Isradipine	Olanzapine	Tacrolimus
Azithromycin	Disulfiram	Itraconazole	Omeprazole	Tamoxifen
Betamethasone	Docetaxel	Ketoconazole	Orphenadrine	Telithromycin
Bortezomib	Doxorubicin	Lansoprazole	Oxybutynin	Teniposide
Bromocriptine	Doxycycline	Lidocaine	Paroxetine	Testosterone
Caffeine	Drospirenone	Lomustine	Pentamidine	Tetracycline
Cerivastatin	Efavirenz	Losartan	Pergolide	Ticlopidine
Chloramphenicol	Enoxacin	Lovastatin	Phencyclidine	Tranylcypromine
Chlorzoxazone	Entacapone	Mefloquine	Pilocarpine	Trazodone
Cimetidine	Ergotamine	Mestranol	Pimozide	Troleandomycin
Ciprofloxacin	Erythromycin	Methadone	Pravastatin	Valproic acid
Cisapride	Ethinyl estradiol	Methimazole	Prednisolone	Venlafaxine
Clarithromycin	Etoposide	Methoxsalen	Primaquine	Verapamil
Clemastine	Felodipine	Methylprednisolone	Progesterone	Vinblastine
Clofazimine	Fentanyl	Metronidazole	Propofol	Vincristine
Clotrimazole	Fluconazole	Miconazole	Propoxyphene	Vinorelbine
Clozapine	Fluoxetine	Midazolam	Quinidine	Voriconazole
Cocaine	Fluvastatin	Mifepristone	Quinine	Zafirlukast
Conivaptan	Fluvoxamine	Mirtazapine	Quinupristin	Ziprasidone
Cyclophosphamide	Fosamprenavir	Mitoxantrone	Rabeprazole	

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John's wort (3)
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate	Repaglinide
Amprenavir	Efavirenz	hydrochloride	Rifabutin
Aprepitant	Eletriptan	Levonorgestrel	Rifampin
Aripiprazole	Enalapril	Lidocaine	Ritonavir
Atazanavir	Eplerenone	Losartan	Saquinavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Sertraline
Benzphetamine	Ergonovine	Medroxyprogesterone	Sibutramine
Bisoprolol	Ergotamine	Mefloquine	Sildenafil
Bortezomib	Erythromycin	Mestranol	Simvastatin
Bosentan	Escitalopram	Methadone	Sirolimus
Bromazepam	Estradiol	Methylergonovine	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Miconazole	Tamoxifen
Buspirone	Estrogens, conj., esterified	Midazolam	Tamsulosin

Busulfan	Estrone	Miglustat	Telithromycin
Carbamazapine	Estropipate	Mirtazapine	Teniposide
Cerivastatin	Ethinyl estradiol	Modafinil	Terbinafine
Chlordiazepoxide	Ethosuximide	Montelukast	Tetracycline
Chloroquine	Etoposide	Moricizine	Theophylline
Chlorpheniramine	Felbamate	Nateglinide	Tiagabine
Cisapride	Felodipine	Nefazodone	Ticlopidine
Citalopram	Fentanyl	Nelfinavir	Tolterodine
Clarithromycin	Flurazepam	Nevirapine	Toremifene
Clobazam	Flutamide	Nicardipine	Trazodone
Clonazepam	Fosamprenavir	Nifedipine	Triazolam
Clorazepate	Fulvestrant	Nimodipine	Trimethoprim
Cocaine	Gefitinib	Nisoldipine	Trimipramine
Colchicine	Halofantrine	Nitrendipine	Troleandomycin
Cyclophosphamide	Haloperidol	Norethindrone	Vardenafil
Cyclosporine	Ifosfamide	Norgestrel	Venlafaxine
Dantrolene	Imatinib	Ondansetron	Verapamil
Dapsone	Indinavir	Paclitaxel	Vinblastine
Delavirdine	Irinotecan	Pergolide	Vincristine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pimozide	Zolpidem
Dihydroergotamine	Isradipine	Pioglitazone	Zonisamide
Diltiazem	Itraconazole	Primaquine	Zopiclone
Disopyramide	Ketamine	Progesterone	

When pazopanib and ARQ 197 are co-administered with compounds classified as ‘inhibitors’, increased plasma concentrations of pazopanib and ARQ 197 are the potential outcomes. The co-administration of ‘inducers’ would potentially lower plasma concentrations of both study drugs. When drugs classified as ‘substrates’ are co-administered with pazopanib or ARQ 197, there is the potential for higher concentrations of the ‘substrate’.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed. Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

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CYP2C8/9 Inhibitors

Amiodarone	Felodipine	Modafinil	Sertraline
Amitryptiline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol (Vitamin D_3)	Indinavir	Pantoprazole	Thioridazine
Cimetidine	Indomethacin	Paroxetine	Ticlopidine
Clopidogrel	Irbesartan	Pentamidine	Tioconazole
Clotrimazole	Isoniazid	Pioglitizone	Tolbutamide
Clozapine	Ketoconazole	Piroxicam	Tolcapone
Cyclosporine	Ketoprofen	Pravastatin	Tranylcypromine
Delavirdine	Lansoprazole	Progesterone	Tretinoin
Dexmedetomidine	Leflunomide	Propafenone	Triazolam
Diclofenac	Losartan	Propofol	Trimethoprim
Diltiazem	Lovastatin	Propoxyphene	Valdecoxib
Dimethyl sulfoxide	Mefenamic acid	Pyrimethamine	Valproic acid
Disulfiram	Meloxicam	Quinidine	Valsartan
Drospirenone	Methimazole	Quinine	Verapamil
Efavirenz	Methoxsalen	Ritonavir	Voriconazole
Entacapone	Metronidazole	Rosiglitazone	Warfarin
Eprosartan	Miconazole	Saquinavir	Zafirlukast
Etoposide	Midazolam	Selegiline	

CYP2C8/9 Inducers

Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

CYP2C8/9 Substrates

Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

When drugs classified as 'substrates' are co-administered with pazopanib, there is the potential for higher concentrations of the 'substrate'. When pazopanib is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of pazopanib is the potential outcome. The coadministration of 'inducers' would potentially lower plasma pazopanib concentrations.

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

CYP2D6 Substrates

Amitriptyline	Diphenhydramine	Maprotiline	Propranolol
Atomoxetine	Dolasetron	Metoclopramide	Protriptyline
Carvedilol	Doxepin	Metoprolol	Risperidone
Chlorpheniramine	Duloxetine	Mexiletine	Tamoxifen
Chlorpromazine	Flecainide	Nortriptyline	Thioridazine
Clomipramine	Fluoxetine	Palonosetron	Timolol
Codeine	Fluvoxamine	Paroxetine	Tolterodine
Desipramine	Haloperidol	Perhexiline	Tramadol
Dextromethorphan	Hydrocodone	Promethazine	Trazodone
Dihydrocodeine	Imipramine	Propafenone	Venlafaxine

When drugs classified as ‘substrates’ are co-administered with pazopanib, there is the potential for higher concentrations of the ‘substrate’.

APPENDIX C: MEDICATIONS THAT MAY CAUSE QTc PROLONGATION

The following table presents a list of drugs that prolong, may prolong, or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.*

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

References:

1. Physician's Desk Reference 2002
2. Facts and Comparisons (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1996

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX E: PATIENT'S MEDICATION DIARY

EXPANSION PHASE, COHORT A, CYCLE 1

Today's date _____ **Agent: Pazopanib, ARQ 197**

Patient Name_____ **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. **Starting on day 1**, you will take **pazopanib** once each day in the morning either 1 hour before or 2 hours after a meal with 1 cup of water.

   Dose: _____. Take ___ 200 mg tablets and ___ 400 mg tablets every day. You should swallow the tablets whole.
   Do not chew, crush, or break the tablets.
3. **Starting on day 8**, you will take **ARQ 197** twice each day, about 12 hours apart, with food. You should swallow the tablets whole. **Do not chew, crush, or break the tablets. You will not take ARQ 197 on days 1-7 of cycle 1**.

   Morning dose: _____. Take ___ 120 mg tablets. Evening dose: _____. Take ___ 120 mg tablets.
4. Record the date, the number of tablets of each size you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of **pazopanib and ARQ 197** tablets when you return for each appointment.
7. You should measure your own blood pressure at home at least once a day (preferably twice a day). If your systolic pressure (top number) is greater than 150 or your diastolic blood pressure (bottom number) is greater than 90, re-measure your blood pressure 1 to 4 hours later. If your systolic pressure is still greater than 150 or your diastolic blood pressure is still greater than 90, please contact your study team for instructions. You should also call the research team if you experience any symptoms of high blood pressure, such as chest pain, shortness of breath, headache, blood in the urine, or double vision.

CTEP Protocol #8880
Clinical Center Protocol #: 12-C-0009

CTEP-assigned Protocol #8880
Local Protocol # _____

Today's date _____ **Agent: Pazopanib, ARQ 197**
Patient Name_____ **Patient Study ID** _____

Day	Date	Pazopanib			ARQ 197				Blood Pressure AM	Blood Pressure PM	Comments
		Time of dose	# of tablets taken		Time of morning dose	# of tablets taken	Time of evening dose	# of tablets taken			
			200 mg	400 mg		120 mg		120 mg			
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Patient's signature _____

APPENDIX F: LVEF DOSE MODIFICATION TABLE

Asymptomatic Decrease in LVEF

The decision to continue or hold STUDY DRUG is based on the LVEF as it relates to the institutions's lower limit of normal (LLN) **and** change in ejection fraction from screening (LVEF as measured at registration) according to the following table:

Relationship of LVEF to institution's LLN	LVEF Decrease < 10%	LVEF Decrease 10-15%	LVEF Decrease ≥ 16%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
≥ 6% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles

Discontinue STUDY DRUG if:

- Two consecutive HOLD catagories occur.
- Three intermittant HOLD catagories occur (at the discretion of the investigator, STUDY DRUG may also be permanently discontinued prior to the occurance of 3 intermittant HOLD catagories).

If LVEF is maintained at a "Continue and repeat MUGA/ECHO" or improves from a HOLD to a "Continue and repeat MUGA/ECHO" category, additonal MUGA scans/echocardiograms prior to the next scheduled MUGA/ECHO will be at the discretion of the investigator.

Symptomatic Cardiac Events

Discontinue STUDY DRUG if:

- A patient has symptoms of congestive heart failure (CHF) and a diagnosis of CHF is confirmed.
- A patient has a myocardial infarction.

APPENDIX G: FACSIMILE TRANSMISSION FORM FOR SAMPLE SHIPMENT

Please use this form to send notification of shipment

From:		**Telephone:**	
Date:		**Fax:**	

To: PPD **Fax:**

Protocol Number:	
Number of samples shipped:	
Date Shipped:	
Expected date of arrival:	
Courier:	
Airway Bill No.:	
Number of packages:	
On dry ice:	Yes / No (Circle one)
Associated hazards:	
Shipped by: (Study Centre Number)	

Please use this form to send notification of shipment

From:		**Telephone:**	
Date:		**Fax:**	

To: Covance Inc. **Fax:**

Protocol Number:	
Number of samples shipped:	
Date Shipped:	
Expected date of arrival:	
Courier:	
Airway Bill No.:	
Number of packages:	
On dry ice:	Yes / No (Circle one)
Associated hazards:	
Shipped by: (Study Centre Number)	