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Reversing Hormone Resistance in Advanced Breast Cancer with Pazopanib

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Study Drug: Pazopanib

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SCHEMA

Registration

↓

Pazopanib 800mg a day by mouth

AND

Letrozole, 2.5 mg a day by mouth **OR** Anastrozole, 1 mg a day by mouth

↓

Scans at 12 weeks and every 16 weeks thereafter (or sooner if clinically indicated)

↓

Continue until progression, withdrawal of consent or unresolved toxicity

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society for Clinical Oncology
AST	aspartate transaminase
AUC	area under the curve
BSA	body surface area
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTC	Common Terminology Criteria
CXR	chest x-ray
DFS	disease-free survival
DLT	dose limiting toxicity
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HGB	hemoglobin
IC/FC	immunomagnetic capture+flow cytometry
ICH	International Conference on Harmonization
IND	investigational new drug application
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MDR	multi-drug resistance
MRI	Magnetic Resonance Imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
PA	posterior-anterior (chest x-ray)
PI	Principal Investigator
PR	partial response
PRC	UCSF Protocol Review Committee
QOL	Quality of Life
RBC	red blood cell
SAE	serious adverse event
ULN	upper limit of normal
WBC	white blood cell

1.0 Background and Rationale

1.1 Background/Standard Therapies

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in women in the United States. Despite a decrease in the overall incidence of breast cancer, more than 40,000 women are expected to die of this disease each year[1]. Despite improvements in therapy, patients with locally advanced or metastatic disease eventually relapse and die from their disease. Investigating treatments aimed at improving outcome is critical, and finding new targeted treatment that could delay disease progression would significantly advance the care of women with this common malignancy.

The majority of breast cancers express receptors for either or both estrogen and progesterone; this finding indicates responsiveness to hormone therapy [2]. For postmenopausal women with hormone-receptor positive advanced stage disease, suppression of estrogen with third generation aromatase inhibitors (AI) is more effective than tamoxifen for first-line endocrine treatment, and AIs have been demonstrated to improve disease free survival compared to tamoxifen in women with early stage, hormone receptor positive disease[3]. However, the major limitation of endocrine therapy remains the near universal development of resistance in the advanced setting, and recurrence despite hormone therapy due to resistance in the early stage setting. Although there are no proven clinical strategies to reverse or prevent endocrine therapy resistance, several pre-clinical investigations suggest opportunities for therapeutic intervention[4]. This trial is designed to evaluate whether anti-VEGF therapy with pazopanib can reverse resistance and prolong progression-free survival when added at the time of progression to endocrine therapy with AIs for hormone-receptor positive metastatic breast cancer.

Angiogenesis and estrogen

Angiogenesis, the formation of new blood vessels, is essential for the development, progression, and metastasis of malignant tumors[5-7]. Vascular endothelial growth factor (VEGF) is a primary stimulus of angiogenesis in tumors and functions through binding VEGF receptor-2 (VEGFR2; also known as flk/kdr) and VEGF receptor-1 (VEGFR1; also known as flt) expressed on endothelial cells[7].

Endothelial cells exposed to the supernatants of estradiol treated breast cancer cells develop increased levels of VEGFR2 compared to controls. This increase in VEGFR2 supports previous findings that endothelial cells containing estrogen receptors exhibit a proliferative response to estradiol[8-10]. In addition, estrogen has been associated with the inhibition of apoptosis of cultured human endothelial cells, and therefore indicates the creation of a pro-angiogenic environment[10].

Estradiol increases intracellular levels of VEGF mRNA and protein in breast cancer cell lines as well as extracellular levels of VEGF protein [11]. Additionally, estradiol treatment of breast cancer cell lines decreased extracellular sVEGFR1, a soluble form of VEGFR1 that is believed to sequester extracellular VEGF and act as an antiangiogenic factor[11, 12]. This decrease was also observed in an *in vivo* xenograft models of breast cancer in nude mice[12].

These data indicate that estrogen acts directly on breast cancer cells to induce angiogenesis by creating a proangiogenic environment. Furthermore, subjects whose tumors have lower sVEGFR1/VEGF ratios tend to have a poorer prognosis compared to those with higher ratios[13, 14]. VEGF may be an important target for hormone receptor-positive breast cancer[15]. In patients with operable breast cancer, neoadjuvant antiestrogen therapy with tamoxifen reduced breast cancer angiogenesis in responding tumors as measured by microvessel count (MVC)[16].

These data support the hypothesis that estradiol can modulate angiogenesis in breast cancer, and that angiogenesis is one mechanism of resistance to hormone directed therapy. Both estrogen and angiogenesis are essential for the development and progression of breast cancer, making the targeting both pathways in combination appealing.

1.2 Investigational Therapy

Pazopanib

Pazopanib is a potent, multi-targeted TKI of VEGFR-1, -2, -3, PDGFR-α and -β and c-kit, with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively[17]. It inhibits VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells (HUVEC) as well as in mouse lungs in a dose-dependent manner. Pazopanib shows significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibits bFGF- and VEGF-induced angiogenesis in two mouse models of angiogenesis, the Matrigel™ plug assay and the cornea micropocket model.

To date, the safety experience includes over 1200 cancer subjects who have been treated in pazopanib studies. Over 850 subjects have received pazopanib monotherapy; the monotherapy safety profile described is based on 225 subjects with renal cell cancer treated with pazopanib. The most common AEs occurring in ≥ 10% of subjects in decreasing order of frequency were diarrhea, fatigue, hair depigmentation, nausea, hypertension, dysgeusia, headache, anorexia, rash, vomiting, abdominal pain, cough, arthralgia, and constipation. Elevations in ALT of any Grade were reported in 50% of subjects with Grade 3 elevations in 6% and Grade 4 in < 1%. AST and ALT elevations occurred in parallel. Hyperbilirubinemia of any Grade occurred in 29% of subjects with Grade 3 elevations in 2%. No Grade 4 elevations have been reported. Concomitant elevations in transaminases and bilirubin have been observed in less than 1% subjects. Uncommon (≤ 1%) but significant adverse events have been reported including: pulmonary embolism, venous thrombosis, hemorrhage, bowel perforation, myocardial infarction/angina, cerebrovascular accidents/TIA, atrial fibrillation, renal failure, and seizures.

Anemia, leukopenia, and thrombocytopenia were reported in 14 – 20% of subjects with Grade 3/4 abnormalities being uncommon (≤ 2%). Hyponatremia of any grade was observed in 32% of subjects; with Grade 3 or 4 hyponatremia in 7% of subjects. Hyperkalemia of any grade was reported in 21% of subjects with Grade 3 or 4 hyperkalemia in 3% of subjects. Hyponatremia and hyperkalemia have not occurred concurrently in the same subject to suggest adrenal insufficiency. Increase in creatinine of any grade was reported in 25% with Grade 3 or 4 events in 1%. Elevations in amylase and lipase of any

grade were reported in 16% and 17% respectively, with Grade 3 events in 1% and 5% respectively. Pancreatitis was reported in one subject. Increase in TSH was reported in 24% and a decrease in T4 in 18% of subjects.

Serial ACTH stimulation tests were conducted in two Phase I and two Phase II trials in cancer subjects. Adrenal insufficiency was not observed in 47 subjects for whom data was available. Twenty one of the 47 subjects had data beyond 24 weeks and 5 had data beyond 52 weeks. Additional pazopanib information is included in the pazopanib investigator brochure (IB).

In October, 2009, the U. S. Food and Drug Administration granted approval to pazopanib tablets (VOTRIENTTM, Novartis Pharmaceuticals) for the treatment of patients with advanced renal cell carcinoma.

The efficacy and safety of pazopanib were evaluated in an international, multicenter, randomized, double-blind trial comparing pazopanib to placebo in renal cell carcinoma who were treatment naïve or who had received prior cytokine therapy. All patients received best supportive care. The trial was conducted in patients with metastatic renal cell carcinoma stratified according to performance status, prior nephrectomy, and prior cytokine therapy.

A total of 435 patients were randomized (2:1) to receive pazopanib (n=290) or placebo (n=145). Demographics were balanced between the two arms. Progression-free survival (PFS) was the trial's primary endpoint. The median PFS was 9.2 and 4.2 months in the pazopanib and placebo arms, respectively (HR = 0.46, p value < 0.001). The effect was observed in both subgroups: treatment naïve (HR = 0.40) and cytokine pre-treated (HR = 0.54). After documented radiological progression, patients receiving placebo could receive pazopanib.

The overall survival results are not mature; 40% of patients had died by the time of data cut-off. The objective response rates were 30% and 3% for pazopanib and placebo, respectively. The median duration of responses was 13.5 months.

The most common adverse reactions (greater than or equal to 20%) were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. Grade 3/4 adverse reactions that differed by greater than or equal to 2% between arms were abnormal hepatic function, diarrhea, hypertension, and proteinuria. QT prolongation has been seen with pazopanib. Laboratory abnormalities occurring in >10% of patients and more commonly (>5%) in the pazopanib arm included increased transaminases, hyperglycemia, leukopenia, hyperbilirubinemia, neutropenia, hypophosphatemia, thrombocytopenia, lymphocytopenia, hyponatremia, hypomagnesemia, and hypoglycemia. Deaths due to serious adverse events include cerebrovascular accident, gastric cancer, gastrointestinal hemorrhage, hemoptysis, bowel perforation, cardiac failure, myocardial infarction, hepatic failure and pneumonia occurred more commonly in the pazopanib arm. Hepatic dysfunction is included as a boxed warning in the product label and two deaths were associated with hepatic failure.

Recently, a phase II trial was designed for patients with metastatic breast cancer, who failed 2-3 prior chemotherapy. Total 20 patients were recruited in this study, 70% were ER+, and all were Her-2/neu negative. Pazopanib monotherapy was given at 800 mg daily. One patient (5%) had a partial response, 11 (55%) had stable disease (SD) [four (20%) with SD > or = 6 months], and seven (35%) had progressive disease as their best response. One (5%) was not evaluable. The median time to progression was 5.3 months. Pazopanib did not cause significant severe toxicity aside from grade 3-4 transaminitis, hypertension, and neutropenia in three patients each (14% each) and grade 3 gastrointestinal hemorrhage in one patient (5%)[18].

Standard therapy for hormone receptor positive metastatic disease.
Randomized phase III trials have demonstrated superiority in terms of response and in some settings TTP, for anastrozole, letrozole and exemestane compared totamoxifen in the first-line metastatic setting[19]. The Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) trial, 668 post-menopausal women (approximately 45% of whom were either ER or PgR positive while 55% had a tumor with unknown ER/PR status) were randomized (1:1) to receive either anastrozole or tamoxifen for the treatment of MBC. Time to progression (TTP) of the subgroup of subjects with hormone receptor positive tumors was 8.9 months for subjects administered anastrozole compared to 7.8 months for subjects treated with tamoxifen (statistical analyses for the sub-populations were not performed). Treatment was well-tolerated in both arms, although the notable adverse events for tamoxifen (thromboembolic events and vaginal bleeding) were significantly lower for subjects in the anastrozole arm[20].

A second Phase III trial randomized 916 patients with treatment naïve metastatic breast cancer (hormone receptor–positive or unknown tumors) to receive letrozole 2.5 mg or tamoxifen 20 mg daily. Treatment with letrozole resulted in a significantly longer median TTP than treatment with tamoxifen (9.4 months vs. 6.0 months, $P < .0001$)[21]. The incidence and severity of AEs were similar for letrozole and tamoxifen arms. Adverse events considered to be related to the study drug were also similar frequency (38% for letrozole and 37% for tamoxifen) and were similar in nature for both arms.

Lastly exemestane was compared to tamoxifen in 371 patients with MBC (182 exemestane, 189 tamoxifen). Overall response rate was greater for exemestane than for tamoxifen treatment (46% v 31%; odds ratio = 1.85; 95% CI, 1.21 to 2.82; P = .005) as was median progression-free survival (PFS) (9.9 months; 95% CI, 8.7 to 11.8 monthsvs. 5.8 months; 95% CI, 5.3 to 8.1 months) [22]. Subsequent trials have demonstrated that hormone therapy is effective in sequence, that the order of therapy is not clearly important, and that the nonsteroidal (letrozole and anastrozole) and steroidal AIs (exemestane) are non-cross resistant. Given the above data, AIs have become a standard hormone therapy for the treatment of post-menopausal women with hormone receptor positive MBC.

1.3 Rationale for the Combination of Aromatase Inhibitor and an Angiogenesis Inhibitor

Angiogenesis, the formation of new blood vessels, is essential for the development, progression, and metastatic growth of malignant tumors [23, 24]. Vascular endothelial

growth factor (VEGF) is a primary stimulus of angiogenesis in tumors and functions through binding VEGF receptor-2 (VEGFR2; also known as flk/kdr) and VEGF receptor-1 (VEGFR1; also known as flt) expressed on endothelial cells [25].

Preclinical research has demonstrated that endothelial cells exposed to the supernatants of estradiol treated breast cancer cells develop increased levels of VEGFR2 compared to controls [26]. This increase in VEGFR2 supports previous findings that endothelial cells containing estrogen receptors exhibit a proliferative response to estradiol [27, 28]. In addition, estrogen has been associated with the inhibition of apoptosis of cultured human endothelial cells, and therefore indicates creation of a proangiogenic environment [28]. *In vitro* studies have revealed that estradiol increases intracellular levels of VEGF mRNA and protein in breast cancer cell lines as well as extracellular levels of VEGF protein [11]. Additionally, estradiol treatment of breast cancer cell lines decreased extracellular sVEGFR1, a soluble form of VEGFR1 that is believed to sequester extracellular VEGF and act as an antiangiogenic factor [11, 12].

The effect of estrogen on angiogenesis was further demonstrated using *in vivo* xenograft breast cancer models [12, 29]. In one study, ovariectomized nude mice bearing slow-release estrogen or placebo pellets were injected subcutaneously with a mixture of MCF-7 cells and Matrigel. The Matrigel–MCF-7 cell plugs were excised after 6 days and VEGFR was analyzed. Levels of VEGFR-1 protein were lower in Matrigel-embedded MCF-7 cells from mice implanted with estrogen pellets than in Matrigel-embedded MCF-7 cells from mice with placebo pellets. This decrease in VEGFR-1 expression was associated with a pronounced increase in the angiogenic response, reflected by a statistically significant increase in vascular density measured in the Matrigel plugs from estrogen-treated mice compared with vascular density measured in the Matrigel plugs from placebo-treated mice [12] . In another xenograft breast cancer model, castration in a male mouse model bearing androgen-dependent breast cancer led to tumor shrinkage and vascular regression. However, endocrine resistance emerged in this tumor model and was heralded by a wave of neovascularization and tumor regrowth. On a molecular level, castration initially causes a reduction in *VEGF* mRNA levels that parallels tumor and vascular regression. At the time of tumor regrowth, *VEGF* mRNA levels simultaneously rebound. Interestingly, castration in this model led to endothelial cell apoptosis before tumor cell apoptosis, supporting a direct effect of endocrine therapy on tumor vasculature. These data indicate that estrogen acts directly on breast cancer cells to induce angiogenesis by creating a proangiogenic environment [29].

In the clinical setting, patients with metastatic breast cancer, who had high VEGF levels in tumor tissue by ELISA , had lower response to first-line endocrine therapy compared with patients who had low VEGF levels in a multivariate analysis ($p=0.025$). In addition, a trend towards shorter PFS ($p=0.075$) was also seen [30]. In a randomized trial of tamoxifen in premenopausal women in the adjuvant setting, the benefits of tamoxifen for 2 years were significantly decreased in patients with high tumor-specific VEGFR2 expression by immunohistochemistry[31].

The addition of antiangiogenic therapy to hormonal therapy has been investigated in several clinical trials. In a phase II single arm study, 27 patients with metastatic breast cancer who progressed on endocrine therapy alone were recruited. Patients were continued on the same hormone therapy to which they had become refractory with the addition of bevacizumab. Stable disease was seen in 18 patients (66%) [32]. In a multi-center feasibility trial performed at MSKCC and UCSF, 43 patients with treatment naïve metastatic ER positive breast cancer, stable or responding to NSAI treatment were treated with the combination of letrozole and bevacizumab. 74% of the patients had clinical benefit with a favorable PFS of 17.1 months compared with a 9- month historical PFS in postmenopausal women with MBC treated with letrozole alone in the first-line setting [33]. This study led to an ongoing Phase III trial with the U.S. cooperative group CALGB testing this combined therapy.

These data suggest that co-targeting the tumor with endocrine therapy as well as its associated vasculature using anti-angiogenic agents could lead to additive effects, resulting in more effective anticancer therapy, and potentially reversing acquired resistance to hormone therapy [34].

In this trial, we propose to evaluate the role of VEGFR blockade with the tyrosine kinase inhibitor pazopanib in combination with nonsteroidal aromatase inhibitors (NSAI) in patients who are progressing or have relapsed on the same NSAI hormone therapy given for advanced or early stage breast cancer. If this trial demonstrates clinical benefit, this all oral combination could be tested in both the neoadjuvant and metastatic settings in a randomized phase II design.

In order to investigate potential factors predicting response or resistance to pazopanib and NSAIs, several translational studies have been incorporated into this trial.

The prognostic value of circulating tumor cells (CTC) has been demonstrated in several studies in breast cancer, especially in advanced stage [35-38]. At UCSF in the laboratory of Dr. John Park, we have demonstrated expertise in the measurement of CTC in patients with advanced stage breast cancer by IC/FC assay. CTC are first enriched with immunomagnetic beads coated with EpCAM, then EpCAM+, CD45-, nucleic acid+ cells are detected by flow cytometry. This technique is highly sensitive and reproducable, and allows sorting of cells for molecular analysis as well as analysis of cell surface markers[39]. In this trial, we will collect patient's peripheral blood samples every 4 weeks while on treatment and follow any reduction of CTC.

The mechanisms of hormonal resistance includes intrinsic and acquired pathways: decreased ER expression accounts for intrinsic resistance and the increased receptor tyrosine kinase pathway relates to acquired resistance [40-42]. We plan to analyze the mutation of PI3K/Akt and deletion of PTEN by sequencing in CTC (depending on numbers of cells, which in turn determines feasibility), in order to make a preliminary assessment of potential markers of response to pazopanib.

The tumor microenvionment plays an important role in cancer development and progression. Clinical studies have revealed that the increased T regulatory cells (Treg), high ratios of

CD4/CD8 T lymphocytes, and extrafollicular B cells in primary tumors correlated with worse overall survival [43-45]. Recently, studies from preclinical models have shown that tumor associated macrophages (TAM) can promote pulmonary metastases in breast cancer animal models, and in both the preclinial and clinical settings are associated with worse clinical outcome [46-48]. TGFβ has been linked to hormonal resistance in breast cancer. The activation of TGFβ leads to increased regulatory $CD4^+$ T cells and decreased cytotoxic $CD8^+$ T cells in the tumor microenvironment [49]. A recent study in non-small cell lung cancer suggestes that baseline and postreatment levels of cytokines, particularly IL-4 and IL-12 correlated with response to pazopanib[50]. In this study, we will collect patients's serum to monitor the level of cytokines at baseline and during treatment, we will compare the change of cytokine level with panzopanib in each patient, and also compare between responders and non-responders. This information may help us to identify biomarkers that would predict response to antiangiogenic therapy and to identify possible mechanisms of resistance.

2.0 Objectives

2.1 Primary Objectives:

- To evaluate the clinical benefit rate (including complete response, partial response, and stable disease) at 12 weeks from the addition of pazopanib to a non-steroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) in patients with hormone receptor positive advanced breast cancer progressing on the same NSAI hormone therapy.

2.2 Secondary Objectives:

- To evaluate progression free survival in patients treated with the combination of pazopanib and a NSAI.
- To evaluate safety of the combination of pazopanib and a NSAI.

2.3 Exploratory objectives:

- To quantify CTC as a surrogate marker of response.
- To evaluate specific markers including estrogen receptor, PI3K/AKT and PTEN on CTC at the time of study entry
- To evaluate the immune signature in serum samples from patients enrolled in this trial, including: IL-6, IL-8, VEGF, sVEGFR2, E-selectin, GRO-1,IL-4, IL-16, IP-10, IL-12, CSF-1, TIMP-1, OPN. HGF, SDF-1a and TRAIL.

3.0 Study Design and Eligibility Criteria

3.1 Study Design

This is a nonrandomized, open label, multicenter phase II trial to evaluate the efficacy of pazopanib in combination with a NSAI in patients with advanced breast cancer.

Patients with metastatic breast cancer progressing or relapsing on a NSAI will be eligible for enrollment in this study. Progression must be documented by radiographic studies. This will be a two-step protocol; 14 patients will be enrolled initially. If at least 1 response (response defined as clinical benefit) is observed in the first 14 patients at 12 weeks, we will proceed to

the second stage, where an additional 13 patients will be enrolled. We plan to enroll a total of 30 patients at 2 sites: UCSF and Yale Cancer Center (Yale), expecting that up to 3 patients will be un-evaluable due to unexpected events.

Treatment will consist of pazopanib, 800 mg a day by mouth and continuation of the NSAI (letrozole, 2.5 mg a day, or anastrozole, 1 mg a day) the patient was taking at the time of progression. This treatment will be continued until progression or toxicity. Dose reduction of pazopanib for toxicity will be allowed. Patients will be evaluated by serial radiographic studies as well as circulating tumor cells. The primary endpoint is clinical benefit rate at 12 weeks.

3.2 Inclusion Criteria

A subject will be considered eligible for inclusion in this study only if all of the following criteria are met:

1. Subjects must provide written informed consent prior to performance of study specific procedures or assessments, and must be willing to comply with treatment and follow up.
    a. Procedures conducted as a part of routine clinical management of the subject (e.g., blood count, imaging study) and obtained prior to signed informed consent may be utilized for Screening or Baseline purposes provided these tests are obtained as specified in the protocol).
2. Subjects must have measurable or evaluable disease. Disease sites that are evaluable for progression but not measurable per RECIST guidelines version 1.1 include:
    a. Bone lesions
    b. Previously irradiated lesions
    c. Cutaneous manifestations (non-discrete lesions only)
3. Age ≥ 18 years.
4. Postmenopausal women defined by one of the criteria:
    a. No spontaneous menses for at least 12 months if the subject is ≥ 50 years old;
    b. Amenorrheic for at least 12 months if the subject is < 50 years old, with serum estradiol within the institutional postmenopausal range;
    c. Bilateral oophorectomy;
    d. If prior hysterectomy but intact ovaries, must be ≥ 55 years old, or have serum estradiol within the postmenopausal range;
    e. If premenopausal, must be on a GnRH agonist (leuprolide or goserelin) with serum estradiol levels within the institutional postmenopausal range.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2.
6. Histologically or cytologically confirmed estrogen receptor (ER) and/or progesterone receptor (PgR) positive carcinoma of the breast with unresectable, locally advanced and/or metastatic (AJCC Stage IV) disease.

7. Subjects must have received prior hormonal therapy for the treatment of breast cancer as follows:
   a. Progression must be documented while taking a nonsteroidal aromatase inhibitor including anastrozole or letrozole.
   b. If hormonal therapy was administered in the adjuvant setting, subjects must have received therapy for at least 6 months prior to developing metastatic disease.
   c. If hormonal therapy was administered in the metastatic setting, subjects must have received therapy for at least 3 months prior to progression
8. Subjects whose tumors overexpress ErbB2 are eligible provided that they have progressed following therapy which included trastuzumab and/or lapatinib.

   ***Note for prior lapatinib*:** Subjects must have completed therapy with lapatinib at least 7 days prior to the first dose of study drug.

   ***Note for prior trastuzumab*:** Subjects who received Q3 weekly, Q2 weekly or Q1 weekly must have completed therapy with trastuzumab at least 3 weeks, 2 weeks or 1 week, respectively, prior to the first dose of study drug.
9. Adequate hematologic and hepatic function as defined in Table 1.

Table 1 Definitions for Adequate Hematologic and Hepatic Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN (except in patients with Gilbert's)
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST) [c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if >1.5 mg/dL: Calculated creatinine clearance	≥30 mL/min
Quantitative urine protein by dipstick	≤100
Urine Protein to Creatinine Ratio (UPC)[d]	≤1

a. Subjects may not have had a transfusion within 7 days of screening assessment.
b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
c. Concomitant elevations in AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted. Bilirubin ≤ 1.5 except if Gilbert's (elevation due to direct bilirubin)
d. A UPC is required only if the urine protein is > 100. If UPC >1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.

10. Subjects must have discontinued hormone replacement therapy (HRT) (e.g., conjugated estrogens tablets, USP or premarin), at least 28 days prior to receiving the first dose of randomized therapy.
11. Radiotherapy prior to initiation of therapy is allowed to a limited area (e.g., palliative treatment for painful bone metastases), if it is not the sole site of disease. Subjects must have completed treatment at least one week prior to starting study drugs, and must have recovered from all treatment-related toxicities.
12. Bisphosphonate or RANK ligand inhibitor therapy for bone metastases is allowed. Prophylactic use of bisphosphonates in subjects without bone disease, except for the treatment of osteoporosis, is not permitted;
13. Ability to swallow and retain oral medication.

3.3 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Prior use of pazopanib or other agents targeting angiogenesis pathway (such as bevacizumab, sunitinib, or sorafenib) in the metastatic setting
2. Premenopausal levels of estradiol, or ongoing menses (see definitions of menopause above).
3. Known central nervous system (CNS) metastases or leptomeningeal carcinomatosis. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if the subject has clinical findings suggestive of CNS metastasis.
4. History of another active malignancy.

   Note: Subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
5. Clinically significant gastrointestinal abnormalities which might interfere with oral dosing, including, but not limited to:
   a. Malabsorption syndrome
   b. Major resection of the stomach or small bowel that could affect the absorption of study drug
   c. Inflammatory bowel disease
   d. Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
   e. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment
6. Presence of uncontrolled infection.

7. Prolongation of corrected QT interval (QTc) >480msecs.
8. History of any one or more of the following cardiovascular conditions within the past 6 months:
    a. Angioplasty or stenting
    b. Myocardial infarction
    c. Unstable angina
    d. Coronary artery by-pass graft surgery
    e. Symptomatic peripheral vascular disease
9. Class II, III or IV congestive heart failure, as defined by the New York Heart Association (NYHA).
10. Use of an investigational agent, including an investigational anti-cancer agent, within 14 days prior to the first dose of study drug.
11. Prior use of an investigational drug that targets VEGF or VEGF receptors.
12. Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity.
13. Poorly controlled hypertension (defined as systolic blood pressure (SBP) of ≥140mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg).

    Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Blood pressure must be re-assessed prior to start of study therapy. The mean SBP/DBP values must be <140/90mmHg (OR 150/90mmHg, if this criterion is approved by Safety Review Team) in order for a subject to be eligible for the study.
14. History of cerebrovascular accident (CVA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.

    Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulant agents for at least 6 weeks are eligible.
15. Major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer not related to cancer (procedures such as catheter placement not considered to be major).
16. Evidence of active bleeding or bleeding diathesis.
17. Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures

4.0 Patient Registration

4.1 Stratification

No stratification will be performed in this study

4.2 Randomization and Blinding

No randomization or blinding will be performed in this study.

4.3 Registration and Enrollment

The Coordinating Center for this study will be UCSF. All patients who are consented will be entered into the UCSF Cancer Center OnCore database, which is password protected and meets HIPAA guidelines. All data will be collected and entered into OnCore® by Clinical Research Coordinators (CRCs) from UCSF and Yale.

Patients can be registered only after the pretreatment evaluation is complete and all eligibility criteria have been met. The patient must have signed and dated the currently approved consent form prior to any study-related screening procedures are performed.

The registration procedure at Yale will be as follows: when the Principal Investigator determines that a patient meets eligibility criteria; the study site will fax or e-mail a completed eligibility checklist and supporting source documentation to UCSF CRC. The CRC will check the forms for completeness and contact Yale regarding any discrepancies. The Study Chair will approve each patient registration by signing the eligibility checklist and will assign a patient number. Upon obtaining signed informed consent, the patient information will be entered into OnCore. UCSF will provide a study-specific patient ID number to Yale. All future study documentation related to that patient should include the assigned patient ID number.

5.0 Investigational Treatment Plan

5.1 Dose and Schedule

Pazopanib, 800 mg a day by mouth

Letrozole 2.5 mg, **OR** anastrozole 1 mg a day by mouth;

5.2 Duration of Therapy

Treatment is continued until progression, withdrawal of consent, or unresolved toxicity.

6.0 General Concomitant Medication and Supportive Care Guidelines

Subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to their screening visit. The investigator must be informed as soon as possible about any new medication taken from the time of screening until the end of the clinical phase of the study (final laboratory sample).

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

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

7.0 Toxicity Management & Dose Modifications

At each visit during the Treatment Period, subjects should first be evaluated for the occurrence of AEs and laboratory abnormalities. The potential causes of the adverse events should be thoroughly investigated and confounding factors should be identified and eliminated whenever possible.

Treatment emergent hypertension or proteinuria is relatively common in subjects receiving pazopanib and is handled by dose modification of pazopanib. Some adverse events, although rare, can result in significant clinical consequence such as arterial/venial thrombosis, severe hemorrhage, bowel perforation and severe fatigue/asthenia, therefore should be promptly identified and managed. Some clinical signs and symptoms may be early indicators for severe toxicity that should be thoroughly investigated (e.g., abdominal pain may be an early sign for bowel perforation).

Specific recommendations for management of these possible AEs along with guidelines for dose delay/modification or discontinuation of study treatment are provided in Tables 2 and 3.

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

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

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

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

Recommendations for investigational product dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 2.

Table 2 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension[a]	
(A). Asymptomatic and persistent SBP of ≥150 and <170 mmHg, or DBP ≥90 and <110 mmHg.	Step 1. Continue investigational product pazopanib at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[b] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Interrupt pazopanib.. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt pazopanib Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC ≥ 3 grams or 24-hr urine protein ≥ 3 grams	Step 1. Interrupt pazopanib. Step 2. Test weekly the 24-hour urine protein until the level is <3 grams. Then, restart pazopanib, dose reduced by 200 mg. Step 3. If 24-hour urine protein ≥ 3 grams recurs, repeat Steps 1 and 2. Step 4. If 24-hour urine protein ≥ 3 grams recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow up per protocol.

Hemorrhage /Bleeding

Grade 1	For hemoptysis, interrupt pazopanib and contact the study PI to discuss whether further treatment with pazopanib is appropriate. Continue pazopanib with current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ Grade 1. Step 2. Restart pazopanib; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.

Venous Thrombosis (DVT, PE)

Grade 1 and 2	Continue pazopanib with same dose; initiate and monitor anticoagulation as clinically indicated.
Grade 3 or >	Discontinue pazopanib and continue follow-up per protocol.
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.

Arterial Thrombosis/Ischemia

Any Grade	Discontinue pazopanib and continue follow-up per protocol.

Thrombocytopenia: Investigate and document underlying cause

Grade 1 or 2	Continue pazopanib with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 2. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol

Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.

Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue IP at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold IP 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart IP with a dose reduction to 400 mg 4. If recurrent consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care	1. Discontinue IP

Other Clinically Significant Adverse Events [c]

Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue pazopanib and continue follow-up per protocol.

Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.

QTc ≥ 480 < 500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥500 msec	Discontinue pazopanib and continue follow-up per protocol.

a. Patients are encouraged to self-monitor BP twice a week
b. Well-controlled BP defined as mean SBP ≤150 mmHg and mean DBP ≤90 mmHg.
c. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4) for the management of treatment related diarrhea, please refer to Appendix III. Abbreviations: BP, blood pressure; PAZOPANIB, investigational product.

Dose Interruptions/Modifications for Hepatotoxicity

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

Table 3 Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x upper limit of normal (ULN)	Continue IP at current dose with full panel liver function tests (LFTs)[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	1. Continue pazopanib at current dose. 2. Work up for other etiologies as clinically indicated. 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1.
(C). ALT >8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash), not attributed to malignancy.	**1st occurrence** 1. Discontinue pazopanib until toxicity resolves to ≤ Grade 1 or baseline. Report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence (section 16.2, SAE reporting), and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. Pazopanib may only be restarted following recovery is toxicity is clearly unrelated to study drug (e.g. alcohol or significant acetaminophen ingestion) 2. Work up for other etiologies as clinically indicated . 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until alanine aminotransferase (ALT)/aspartate aminotransferase (AST) reduced to Grade 1.

Event	Dose Modification Algorithms
(D). ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin <2.0 x ULN; with direct bilirubin >35%) not related to disease progression, or with hypersensitivity symptoms (e.g., fever, rash).	1. Discontinue pazopanibpazopanib immediately, report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence (section 16.2, SAE reporting), and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. 2. Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: • Eosinophil count • Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus IgM antibody, or heterophile antibody, or monospot testing) • Anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody • Serum creatinine phosphokinase for possible muscle injury caused LFT elevation • Liver imaging (ultrasound or CT scan) 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until LFTs reduced to Grade 1.
For isolated total bilirubin elevation without concurrent ALT increases (defined as ALT < 3 X ULN)	1. Isolated hyperbilirubinemia (ie in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. 2. If bilirubin is > 2 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If the bilirubin is predominantly indirect (unconjugated), continue pazopanib at the same dose. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

8.0 Schedule of Assessments

The study-specific assessments are detailed below and are outlined in the Schedule of Assessments Table. Screening assessments must be performed within 21 days prior to the first dose of investigational product (unless otherwise specified). Screening assessments performed within 7 days of dosing may also be used as Day 1 assessments. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 7 days unless otherwise noted. Treatment or visit delays due to public holidays, weather conditions, or natural disasters, do not constitute protocol violations.

A signed, written, informed consent form must be obtained prior to screening assessments, and before any study-specific assessments are initiated.

Schedule of Assessments

Period/Procedure	**Screening1**	**Treatment**						**Follow-Up**
Week or Day **Study Day**	-21 to -1	Day 1	Every 2 weeks (until week 4)	Week 4 only	Every 4 weeks[2]	Week 12 only	Every 16 weeks (after week 12)	End of Study Follow-up Assessments
Informed Consent	X							
Randomization	N/A							
Treatment								
Study drug		Study drug is taken orally once a day						
Clinical Procedures								
Medical History	X		X					
Physical Exam with weight	X	X	X		X			X
Vital Signs	X	X[3]	X		X			X
Disease Assessment[4]	X					X[5]	X[5]	X
ECOG Performance Status	X	X	X		X			X
EKG with QTc measurement	X			X		X	X	X
Laboratory Assessments[6]	X				X			X
Liver Function Tests (LFT)[7]	X		X[7]		X[7]			
Urinalysis	X				X			
Quantitative dipstick for urine protein[8]	X				X			
Thyroid function (TSH, free T3 and free T4)	X							
Blood for CTC[9]	X			X		X		X
Blood for cytokines[10]	X			X				
Archival tumor tissue collection	X							
Tissue biopsy, *Optional*[11]	X							
Other								
Adverse Event Assessment		X	X		X			X
Con Meds	X	X	X		X			X

[1] All screening and baseline procedures must be completed within 21 days prior to the first dose of study medication

[2] If stable without grade 2 or greater toxicity

[3] Subjects must have a pre-dose BP reading of ≤ 150/90mmHg

[4] CT of chest, abdomen and pelvis for subjects with measurable disease; CTMRI or Bone scan for subjects with bone only disease; Bone scan to be performed on all patients at screening. PET/CT can be used in place if CT scan is diagnostic

[5] Unless indicated sooner by clinical findings

[6] Blood urea nitrogen (BUN), Creatinine, Calcium, Potassium, Sodium, Glucose, Hematology: Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White blood cell count (WBC), and differential are collected every 2 weeks until week 4, then every 4 weeks

[7] Liver Function Tests (LFT) including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase, Total Bilirubin and Albumin. Hematology: Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White blood cell count (WBC), and differential. LFTs are collected every 2 weeks at weeks 3, 5, 7, and 9, then every 4 weeks and as clinically indicated.

[8] UPC is required only if urine protein is > 100.

[9] CTCs will be collected at baseline, and then at 4 weeks, at 12 weeks and at the first visit documenting progression. One CellSave tube (7.5 ml) and one purple top tube (10 ml) should be sent at baseline, subsequent collections should include only one CellSave tube. Quantification of CTC will be conducted at Dr. John Park's laboratory at UCSF

[10] Serum will be collected at baseline and at 4 weeks. The cytokine levels will be measured by ELISA.

[11] Tissue biopsy is optional in this study, the safety of the biopsy will be determined by treating physicians.

8.1 Screening Assessments

Eligible patients will have the following procedures performed within 3 weeks prior to study entry:

1. Medical history.
2. Physical examination including height (recorded only at baseline) and body weight.
3. Vital signs
4. Disease assessment (CT of chest, abdomen and pelvis for subjects with measurable disease; CT/MRI or Bone Scan for subjects with bone only disease, or PET/CT). Bone scan to be performed on all patients at screening. PET/CT can be used in place if CT scan is diagnostic.
5. ECOG Performance Status
6. EKG with QTc measurement
7. Laboratory assessments including:
   a. Clinical chemistry laboratory tests: Blood urea nitrogen (BUN), Creatinine, Calcium, Potassium, Sodium, Glucose, and
   b. Hematology: Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White blood cell count (WBC), and differential.
8. Liver Function Tests (LFT) including:
   a. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase, Total Bilirubin and Albumin.
9. Urinalysis with quantitative protein by dipstick. If > 100 by dipstick a UPC must be performed.
10. Thyroid function (TSH, free T3 and free T4).
11. Blood for circulating tumor cells.

a. One 7.5 ml CellSave tube, and one 10 ml purple top tube

12. Blood for cytokines
13. Archival tumor tissue collection: Paraffin-embedded tissue either at the time of diagnosis or disease relapse
14. Record all medication(s) received within 30 days prior to the first dose of study treatment and note if the medication is ongoing.

8.2 Pre-dose Assessments on Day 1

1. Physical examination (including body weight)
2. Vital signs (Subjects must have a pre-dose BP reading of ≤150/90mmHg)
3. ECOG Performance Status
4. AE/SAE Assessments
5. Concomitant Medications

8.3 Assessments During Treatment Period

8.3.1. Every 2 weeks until week 4

1. Medical History
2. Physical Exam including weight
3. Vital Signs
4. ECOG Performance Status
5. Adverse Event Assessment
6. Con Meds

If stable without grade 2 or greater toxicity, visits can be decreased to monthly after the first 4 weeks of therapy.

8.3.2. Every 2 weeks (weeks 3, 5, 7, and 9) until week 9

1. Liver Function Tests (LFT) including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase, Total Bilirubin and Albumin.

8.3.3. Week 4 only

1. 12-Lead EKG
2. Blood for CTC. One CellSave tube (7.5 ml) will be drawn.
3. Blood for cytokines

8.3.4 Every 4 weeks

1. Physical Exam including body weight
2. Vital Signs
3. ECOG Performance Status
4. Laboratory assessments including:
   a. Clinical chemistry laboratory tests: Blood urea nitrogen (BUN), Creatinine, Calcium, Potassium, Sodium, Glucose, and
   b. Hematology: Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White blood cell count (WBC), and differential.
5. Liver Function Tests (LFT) including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase, Total Bilirubin and Albumin.
6. Urinalysis with quantitative protein by dipstick. If > 100 by dipstick a UPC must be performed.
7. Adverse Event Assessment
8. Con Meds

8.3.5 Week 12 only

1. Blood for CTC. One CellSave tube (7.5 ml) will be drawn.
2. Disease assessment (CT of chest, abdomen and pelvis for subjects with measurable disease [unless indicated sooner by clinical findings] or Bone Scan for subjects with bone only disease, or PET/CT). PET/CT can be used in place if CT scan is diagnostic.
3. 12-Lead EKG

8.3.6 Every 16 weeks (after week 12)

1. Disease assessment (CT of chest, abdomen and pelvis for subjects with measurable disease [unless indicated sooner by clinical findings] or Bone Scan for subjects with bone only disease, or PET/CT). PET/CT can be used in place if CT scan is diagnostic.
2. 12-Lead EKG

8.4 Follow-Up Assessments

The following assessments will be performed following completion of study treatment.

1. Physical examination including body weight.
2. Vital signs
3. Disease assessment (CT of chest, abdomen and pelvis for subjects with measurable disease; CT/MRI or Bone Scan for subjects with bone only disease, or PET/CT) PET/CT can be used in place if CT scan is diagnostic.
4. ECOG Performance Status.
5. 12-Lead EKG
6. Laboratory assessments including:
   a. Clinical chemistry laboratory tests: Blood urea nitrogen (BUN), Creatinine, Calcium, Potassium, Sodium, Glucose, and Hematology: Hematocrit (HCT)
   b. Hematology: Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White blood cell count (WBC), and differential.
7. Blood for CTC at the first visit documenting disease progression if measurable ONLY. One CellSave tube (7.5 ml) will be drawn.
8. Record any AE(s) and SAEs and assign appropriate grade (NCI CTCAE v4).
9. Record all concomitant medications(s) added and/or changed.

Patients will be followed for four weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

8.5 Correlative studies:

1. CTC quantification: peripheral blood will be collected for CTC at baseline, at 4 weeks and 12 weeks, then at the first visit documenting disease progression.
2. Evaluate PI3K/AKT and PTEN mutation on archival tissue sample and fresh tissue if available: PI3K/AKT and PTEN mutation will be tested on paraffin-embedded tumor tissue by DNA sequencing, this data will be compared to the mutation study obtain from CTC at the time of study entry and during the treatment.
3. Exploratory analysis of CTC will be undertaken depending on the number of CTCs for:
   a. Estrogen receptor
   b. PI3K/AKT and PTEN
   c. Other genes based on availability of DNA and RNA and depending on the gene panel utilized for this trial
4. Changes in immune signature: serum will be collected within two weeks of study start and at 4 weeks. Immune signature (cytokines and chemokines) including: IL-4, IL-16, IP-10, IL-12, CSF-1, TIMP-1, OPN. HGF, SDF-1a and TRAIL will be measured by ELISA (Appendix IV)

9.0 Criteria for Evaluation

9.1 Response Definitions

Measurable Lesion: Bidimensionally measurable, with clearly defined margins on physical exams, x-ray, or scan. At least one diameter must be greater than 0.5 cm. Bone lesions are not included.

Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined, palpable nodal disease, lesions with both diameters less than .5 cm, bone disease. Markers which have been shown to be highly correlated with extent of disease are also considered evaluable.

Non-Evaluable Disease: Pleural effusions, ascites, disease documented by indirect evidence only (e.g., by lab values which don't qualify as evaluable).

Objective Status: To be recorded at each evaluation: If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. If patient has effusions, ascites or disease assessable by surgical restaging (e.g., testicular and extragonadal germ cell cancer), disease must be cytology negative. Patients with markers or indirect evidence of involvement must have normalization of abnormal values. All measurable, evaluable and non-evaluable lesions and sites must be assessed.

Partial Response (PR): Applies only to patients with at least one measurable lesion greater than or equal to 50% decrease under baseline in the sum of the products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed

Stable: Does not qualify for complete response, partial response or progression. All measurable and evaluable sites and lesions must be assessed.

Progression: 25% increase or an increase of 10 sq. cm (whichever is smaller) in the sum of products of measurable lesions over smallest sum observed (over baseline if no decrease), OR appearance of any lesion which had disappeared, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to deteriorating condition (unless deterioration is clearly unrelated to this cancer). For scan only bone disease, increased uptake does not constitute clear worsening and new lesions are required for progression. Worsening of existing non-evaluable disease does not constitute progression.

Best Response: This will be calculated from the serial evaluation of objective status. For patients with all disease sites assessed every three to six weeks, two objective determinations of CR, will be required for a best response of CR; two of PR or better, but not qualifying for CR, will be required for PR; two of stable or better, but not qualifying as PR or CR, will be required for stable; and patients with objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease.

9.2 Toxicity Definitions

All study toxicities will be graded by the NCI Common Terminology Criteria Version 4.0.

10.0 Criteria for Termination

10.1 Conditions for Terminating the Study

The Study Chair may terminate the study for any of the following reasons:

- Significant toxicities
- If it becomes clear that the study treatment is less effective than standard treatment
- Once all data have been completed.

10.2 Conditions for Individual Patient Termination

The Principal Investigator at each site may terminate the participation of an individual patient for any of the following reasons:

- Disease progression
- Need for exclusionary concurrent treatment
- Withdrawal of informed consent
- Protocol non-compliance
- Lost to follow-up.

11.0 Drug Information

11.1 Drug Name
Pazopanib.

11.1.1 Mode of Action
Pazopanib is a novel compound being developed for the treatment of various cancers. Pazopanib is a potent, multi-targeted TKI of VEGFR-1, -2, -3, PDGFR-α and -β and c-kit, with IC50 values of 10, 30, 47, 71, 84 and 74 nM, respectively inhibits VEGF induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells (HUVEC) as well as in mouse lungs in a dose-dependent manner. Pazopanib shows significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibits bFGF- and VEGF-induced angiogenesis in two mouse models of angiogenesis, the Matrigel plug assay and the cornea micropocket model.

11.1.2 Shipment, Storage and Stability
Investigational product must be dispensed or administered according to procedures described herein, and in accordance with procedures at each participating site. Study drugs will be shipped from the drug manufacturer directly to the participating sites for direct distribution of the drugs to the study patients. The participating site will be responsible for drug accountability at their site. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only the site pharmacist or authorized site personnel may supply or administer investigational product. Investigational product will be dispatched to the site only after receipt of required documents in accordance with applicable regulatory requirements and Novartis Pharmaceuticals procedures.

Investigational product(s) will be dispensed to the subject on Day 1 after it has been confirmed that the subject meets all eligibility criteria and all screening assessments have been completed and the results reviewed. Subjects are to return to the site approximately every 4 weeks for re-supply of investigational product(s).

11.1.3 Dosage and Administration
Pazopanib tablets are supplied as different strengths as summarized in the table below:

Strengths (mg as free base)	Description	
	Color	Shape
50	white to off-white	round
200	white	oval
	gray or pink	capsule-shaped, may be debossed
400	white	oval
	white or yellow	capsule-shaped, may be de-bossed

Placebo tablets to match the round 50 mg tablets and the oval-shaped 200 mg and 400 mg tablets are available.

The tablets are packaged in white high density polyethylene (HDPE) bottles with white plastic, induction seal, child-resistant caps.

Powder for Oral Suspension

Panzopanib Powder for Oral Suspension (PfOS) is a white to slightly colored powder supplied as multiple-dose formulation in amber glass (USP Type III) bottles with childresistant, polypropylene closures. Each bottle contains panzopanib (monohydrochloride salt) equivalent to 5 g of free base. A Placebo to Match panzopanib PfOS is available. The Placebo visually matches the active GW786034B PfOS. The Placebo contains the same excipients as the multiple-dose PfOS, and also contains microcrystalline cellulose, titanium dioxide, magrogol/polyethylene glycol 400, and polysorbate 80 to aid the visual blinding.

The PfOS formulations have been manufactured for use in clinical studies for adults and pediatric oncology patients.

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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

11.1.4 Incompatibilities

Concomitant Medications and Non-Drug Therapies
If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis Pharmaceuticals and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

Permitted Medications
All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.
All concomitant medications taken during the study will be recorded in the electronic case report form (eCRF) with indication, dose information, and dates of administration.

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

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

Permitted Medications – Use with Caution

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

Specific recommendations regarding hypoglycemic therapy including insulin:
Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib [51]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

Effects of Concomitant Pazopanib and Simvastatin
A potential interaction with concomitant administration of 800 mg of pazopanib and simvastatin has been indentified in oncology studies. Pooled data from 11 clinical studies in which cancer patients received pazopanib monotherapy revealed that the incidence of ALT elevation >3 X ULN increased with concomitant pazopanib and simvastatin therapy (11/41 patients; 27%) compared with the incidence with pazopanib and no concomitant statin therapy (126/895 patients; 14%). Due to the lower systemic exposures achieved with both eye drops and low-dose oral pazopanib tablets, and the frequency of liver function monitoring, the use of simvastatin or other statins has been permitted during clinical trials.

The Effects of Pazopanib on Other Drugs
In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2A6, CYP2B6, and CYP2E1. Pregnane

X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 *in vivo*, but had no clinically relevant effect on CYP1A2, CYP2C9 or CYP2C19 metabolism. Therefore, concomitant use of pazopanib with certain medications (substrates of CYP3A4, CYP2C8, and CYP2D6) with a narrow therapeutic window should be undertaken with **CAUTION** due to the potential for alterations in the pharmacologic effects of these medications or an increased risk for serious or life threatening adverse events associated with such medications (see below) secondary to the inhibition of specific CYP enzymes by pazopanib. In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of pazopanib due to its long half-life (i.e., mean 30.9 hours); therefore, continue to exercise **CAUTION** for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications. These medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

In this trial, treatment with these medications while on study treatment is prohibited.

The Effects of Other Drugs on Pazopanib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Furthermore, *in vitro* data suggest that pazopanib is a substrate for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**. Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction to 400 mg pazopanib should be considered when it must be co-administered with strong CYP3A4 inhibitors.

Strong CYP3A4 inhibitors include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)

- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone
- Diet: grapefruit, seville oranges, starfruit, and their juices

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

Drugs that induce CYP3A4 and may decrease pazopanib plasma concentrations include (but are not limited to):

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Prohibited Medications

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

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **7** days prior to the first dose of study drug until discontinuation from the study. **Strong CYP3A4 inhibitors include (but are not limited to)**:

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone
- Diet: grapefruit, seville oranges, starfruit, and their juices at or near time of drug ingestion

11.1.5. Side Effects

See Section 7.0

12.0 Statistical Considerations

The response rate with no additional treatment in women with disease progression while receiving aromatase inhibitors is expected to be <5%. We will consider an overall response rate of 20% to be clinically meaningful. For the purpose of this study, response will be defined as clinical benefit rate, including complete response, partial response, and stable disease for at least 12 weeks.

Therefore, we used the American Cancer Society's website (http://cryptnet.net/kepner/one_sample.html) for a 2 stage design with p0=0.05, p1=0.20 and power 80% at alpha=5%. This design specifies that if 0 of the first 14 eligible and evaluable subjects do not respond to the treatment at 12 weeks, then we are unlikely to reach a true overall response rate of 20%. The 15th patient will not be enrolled until we have confirmed that we have met criteria of at least 1 responses (response defined as clinical benefit) observed in the first 14 patients, to proceed to the second stage. An additional 13 patients will be enrolled in stage 2 for a total of 27 patients. If at least 4 of the total patients respond, we will conclude that the addition of pazopanib in this setting has the possibility of reversing resistance to hormone therapy with aromatase inhibitors. Using this design, we will have a less than 5% chance of incorrectly accepting the null hypothesis (alpha 0.05), and an 80% chance of correctly rejecting the null hypothesis (beta 0.2).

To determine whether the level of cytokines at baseline and during treatment could predict response to antiangiogenic therapy, we will divide patients into two groups; responder and non-responder group. The student t test will be used to analyze the differences of cytokine levels at baseline and at 4 weeks between these 2 groups.

CTC quantification data will be correlated with response and time to progression.

We will make preliminary observations regarding mutations or deletions in PIK3CA and PTEN in patients with measurable CTC, correlating changes with response and disease history, as well as presence or absence of these alterations in archival tumor tissue.

12.1 Endpoint Definitions

Primary endpoint:

- The primary endpoint of this study is clinical benefit (including complete response, partial response, and stable disease) of at least 12 weeks.

Secondary endpoint:

- PFS: evaluate progression free survival in patients treated with the combination of pazopanib and a NSAI in this trial
- Safety : adverse events, SAEs

Exploratory endpoints:

- Evaluate the impact of the combination of pazopanib and a NSAI on circulating tumor cells
- Evaluate the change of immune profile with the combination of pazopanib and a NSAI

12.2 Accrual Objectives

This will be a two stage design with 14 patients enrolled in the first stage. If at least one patient responds (response defined as clinical benefit), an additional 13 patients will be

enrolled for a total of 27 patients. Expecting that approximately 3 patients will be un-evaluable due unexpected events, a total of 30 patients will be enrolled in the protocol.

All patients who take at least two weeks of study drug and the non-steroidal aromatase inhibitor will be evaluable for toxicity and efficacy. Depending on accrual, patients who stop study therapy within the first two weeks may be replaced.

12.3 Estimated Duration of Study

Enrollment will occur over 18 months.
Follow-up 6-8 months after last subject enrolled

12.4 Data and Safety Monitoring

Review of adverse events and serious adverse events (defined below) will be done at Site Committee meetings at UCSF and during monthly teleconferences with Yale. In addition, toxicity reviews will occur once a month in the Breast Oncology Program Site Committee meetings at UCSF. We will hold enrollment to review the safety data after the 5th patient has been on pazopanib for 2 weeks and resume once the study is deemed to be safe. The Study Chair will notify Yale of the enrollment hold.

The UCSF DSMC will monitor the study at UCSF and the Yale DSMC will monitor the study at Yale. The Data and Safety Monitoring reports from Yale will be audited by the Quality Assurance, Compliance, and Safety Committee (QUACS) as they are generated from the monitoring reports for the Yale Site.

12.5 Analyses Timepoints

After the first 14 patients have completed 12 weeks of treatment.
12 weeks after the last patient has been enrolled.

12.6 Sample Size

With 30 patients enrolled, we expect 27 for evaluation at 12 weeks. The two-stage design has 80% power to detect clinical benefit (defined as complete or partial response of stable disease) in 20% of patients compared to <5% of patients without this treatment.

12.7 Replacement Policy

30 patients will be enrolled for a final estimated study sample size of 27. Patients stopping therapy before 2 weeks will be replaced after discussion with the Study Chair.

13.0 Data Forms & Submission Schedule

Patients will be evaluated in clinic at least once per cycle of treatment. All collected data will be entered into template forms in OnCore within one week of each patient visit.

14.0 Special Instructions

None

15.0 Ethical Aspects

15.1 Regulatory Considerations

This study will be reviewed by the UCSF and the Yale IRBs as described below. At UCSF, the protocol will also be reviewed by the Helen Diller Family Comprehensive Cancer Center Protocol Review Committee prior to IRB submission. In addition, UCSF will file an Investigational New Drug application with the FDA as described below.

Independent Ethics Committees/Institutional Review Board

This protocol and the informed consent will be approved by the Committee on Human Research (CHR) (UCSF's IRB). Once approved, the protocol will be reviewed by the Yale School of Medicine Human Investigation Committee. The Principal Investigator at each site is responsible for keeping the IRB apprised of the progress of the study and of any changes made in the protocol prior to implementation. The Principal Investigator at each site will also keep his/her own IRB informed of any significant adverse reactions and any protocol exceptions or deviations. Records of all study review and approval documents must be kept on file by the Principal Investigator at each site, and copies of IRB documentation from Yale will be forwarded to UCSF. All records are subject to FDA inspection during or after completion of the study. The IRBs will receive notification of the termination of the study.

Protocol and Protocol Amendments

Protocol and protocol amendments will be submitted to and approved by the UCSF Protocol Review committee (PRC), in addition to CHR, prior to implementation at UCSF.

It is the responsibility of the UCSF Study Chair (or designee) to distribute the protocol and the protocol amendments to Yale upon IRB approval at UCSF. The protocol may be distributed via e-mail or private courier with confirmation of receipt.

Upon approval of the protocol or protocol amendment by Yale's IRB, a copy of the approval documentation must be submitted to Study Chair. All protocol amendments are expected to be approved by Yale's IRB within 90 days of receipt.

Documentation of Yale's protocol approvals will be maintained in the correspondence files by the Study Chair or designee, and provided to the UCSF centralized regulatory staff. It is the responsibility of the Study Chair to review these documents to ensure that the participating sites are using the current protocol version.

Prestudy Documentation at Participating Sites

Before the study may be initiated at Yale, the following documentation must be submitted to UCSF:

- Copy of the official IRB approval letter for the protocol and informed consent form
- IRB membership list
- Form FDA 1572, signed and dated by the Principal Investigator.
- Current curricula vitae and medical licenses of the site's Principal Investigator and all sub investigator(s) listed on Form FDA 1572.
- Contact information (email, phone number, address) for the research pharmacist and designated contact person(s) (CRC and/or nurse) assigned to this study.
- CAP and CLIA Laboratory certification and institution lab normal values
- Executed clinical research contract

Investigational New Drug Application (IND)

The Coordinating Center (UCSF) is responsible for the preparation and submission of the Investigational New Drug Application (IND) to the FDA. An electronic file (PDF) of all FDA correspondence concerning the IND will be maintained in OnCore, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System. It is the responsibility of the Study Chair to keep the regulatory staff informed of any communications with FDA that affect the status of the IND.

Coordinating Center Documentation

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (as applicable). The UCSF Helen Diller Family Comprehensive Cancer Center recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, sub sites, etc.).

- Correspondence file: should contain copies (paper or electronic) of all protocols and protocol amendments, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.
- Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol and its updates and safety information are distributed.

16.0 Reporting Adverse Drug Reactions

16.1 Adverse Event Definitions

16.1.1 Clinical Adverse Events

A clinical adverse event is any unfavorable or unintended sign, symptom or disease temporally associated with the use of the study drug occurring in a research patient treated with the study drug during treatment or post-treatment follow-up period, regardless of causality assessment. This includes adverse clinical or laboratory findings, intercurrent illness, or an exacerbation or progression of a disease/condition present at baseline.

An adverse event is unexpected if it is not listed in the current labeling for the study drug. An adverse event is considered non-serious if it does not meet any of the serious criteria below.

16.1.2 Laboratory Adverse Events

Laboratory test value abnormalities will not be recorded as adverse events unless they are designated as serious, require treatment, or cause premature withdrawal.

16.1.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- death,
- life-threatening (places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred),
- inpatient hospitalization or prolongs existing hospitalization,
- persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions),
- birth defect/congenital anomaly,
- or any important medical event that may not result in prior listed outcomes but, based upon appropriate medical judgment, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the prior listed outcomes.

16.1.4 Treatment of Investigational Product Overdose

No maximum tolerated dose (MTD) was reached in the dose escalation study of pazopanib administered as a single agent at repeated doses of up to 2000mg/day (Study VEG10003). Systemic exposure to pazopanib at steady-state appeared to plateau at doses greater than 800 mg once daily. Increases in the daily pazopanib dose above 800 mg in the fasted state resulted in a small or no increase in mean systemic exposure to pazopanib.

In the event of pazopanib overdose (defined as administration of more than the protocol-specified dose), the Study Chair should contact the Novartis Pharmaceuticals Study Physician. If the event takes place at Yale, the Principal Investigator will immediately notify the Study Chair.

Decisions regarding pazopanib dose modifications or interruptions will be made by the Study Chair in consultation with the Novartis Pharmaceuticals Study Physician, and with the Yale Investigator, if applicable, based on the clinical evaluation of the subject.

Following an overdose, additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered. A plasma sample for pharmacokinetic analysis for pazopanib and NSAI may be requested by the Novartis Pharmaceuticals Study Physician on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 7 days from the date of the last dose of study drug.

Information regarding the quantity of the excess dose, as well as the duration of overdosing, should be documented in the eCRF.

NSAI overdose is very rare; currently there is no standard guideline on the management of NSAI overdose.

16.2 Adverse Event Reporting Procedures

16.2.1 Data and Safety Monitoring Plan

Oversight and Monitoring Plan

The UCSF- Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study at UCSF includes:

- Review of subject data
- Review of suspected adverse reactions considered “serious”
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly audit

At Yale, monitoring takes place after the first two patients and then 10% annually thereafter. The monitoring plan is set at the scientific review committee meeting as determined by the local PRC (Protocol Review Committee).

Monitoring and reporting Guidelines

All institutional Phase 2 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss at monthly study group or site committee meetings at UCSF, and during monthly teleconferences with Yale. At UCSF Site Committee, the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include the number of patients, significant toxicities as described in the protocol, doses adjustments, and observed responses. All grade 3 or above AEs and SAEs will be entered in the UCSF Helen Diller Family Comprehensive Cancer Center CTMS database.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Review and Oversight Requirements

Adverse Event Monitoring

Adverse Events (AEs) will be recorded on the UCSF Helen Diller Family Comprehensive Cancer Center CTMS database, all grade 3 and above expected and unexpected AEs will be recorded and updated at each visit.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within **10 business days** of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within **1 business day**. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within **1 business day** from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within **1 business day** of this notification. The contact may be by phone or e-mail.

16.2.2 Serious Adverse Event Reporting

Serious Adverse Event reporting will be in accordance with the UCSF-Committee on Human Research and the Yale School of Medicine Human Investigation Committee guidelines and Code of Federal Regulation Title 21 Volume 5 Part 312.32.

UCSF CHR website for guidance in reporting serious adverse events
http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.pdf

FDA website for guidance in reporting serious adverse events
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

MedWatch forms and information:
http://www.fda.gov/medwatch/getforms.htm

Serious Adverse events will be reported on the MedWatch form. The date the SAE was sent to all required reporting agencies will be documented on the UCSF Helen Diller Family Comprehensive Cancer Center CTMS database.

Participating Sites Reporting to Study Chair (UCSF)

In addition to complying with all applicable regulatory reporting laws and regulations, each site will report the following information in writing to the Sponsor-Investigator within one business day of the Investigator's awareness of occurrence:

- All SAEs
- Reports of pregnancy exposure (pregnancy encompasses the entire course of pregnancy and delivery, perinatal and neonatal outcomes, even if there were no abnormal findings; both maternal and paternal exposure is collected);
- Reports of lactation exposure;
- Overdose (with or without an SAE);
- Abuse (use for non-clinical reasons with or without an SAE);
- Inadvertent or accidental exposure; and
- Follow-up information regarding any of the above.
- The participating investigator should include his or her assessment of the causal relationship between each SAE and the Grantor product.

Reports will include the cover page provided, and reference the Protocol Number.

A copy of the report should be sent to the coordinating center CRC at UCSF. Information will be provided.

Study Chair (UCSF) AE reporting to Novartis Pharmaceuticals

Any serious adverse events which occur during the clinical study or within 5 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the Study Chair. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 weeks	Pregnancy Notification Form	2 weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				

ALT: >3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥2.0 x ULN with direct bilirubin >35%) **or with** hypersensitivity symptoms (e.g., fever, rash).	24 hours	SAE data collection tool. [b]Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. [b]Updated Liver Event CRF
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	24 hours	SAE data collection tool. Liver Event CRF[b]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[b]

a. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2.0 x ULN, then the event should be promptly reported as defined.
b. Liver event documents should be completed as soon as possible.

All Events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by **fax within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets.**

- Novartis DS&E Oncology Department - [redacted]

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

Review of Adverse Event Rates

If the study has an increase of unexpected or expected Adverse Event grade 3 or 4 above the rate reported in the Investigational Brochure or package insert, the increase rate of AEs will be reported by the Study Chair to the UCSF DSMC at the time of Identification. The UCSF DSMC Chair and Study Chair will discuss the finding and proceed with a written course of action. If at any time the Study Chair stops enrollment or stops the study due to safety issues the UCSF DSMC Chair must be notified within 24 business hours via e-mail. The UCSF DSMC must receive a formal letter within 10 business days and the CHR must be notified.

If any of the above action occurs in a multiple-institutional clinical trial coordinated by the UCSF-CCC, the Study Chair will insure that all participating sites are notified.

Data and Safety Monitoring Committee Contacts:
DSMC Chair: [redacted]
[redacted] [redacted]
Email [redacted]
Box [redacted]

DSMC Monitors
Box 0128

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18.0 Appendices

Appendix I: ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix II:

NCI CTCAE v4

Appendix III: management of GI toxicity:

Diarrhea

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

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel pattern should be established so that changes in that pattern can be identified. In addition, subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

Diarrhea

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

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

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

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

Experience thus far suggests that, when pazopanib is used as monotherapy, uncomplicated CTCAE Grade 1 or 2 diarrhea may ensue. In rare cases, subjects treated with monotherapy pazopanib may develop debilitating and potentially life-threatening diarrhea with dehydration, renal insufficiency, and electrolyte imbalances. The pathophysiologic mechanism of diarrhea with pazopanib is not known.

The following broad general management principles are recommended as means by which a subject with diarrhea may avoid more serious complications. Guidelines such as these should never replace sound clinical judgment. Standardized and universal guidelines have been

developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea [Benson, 2004]. The guidance provided here is a modification of the ASCO guidelines.

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

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

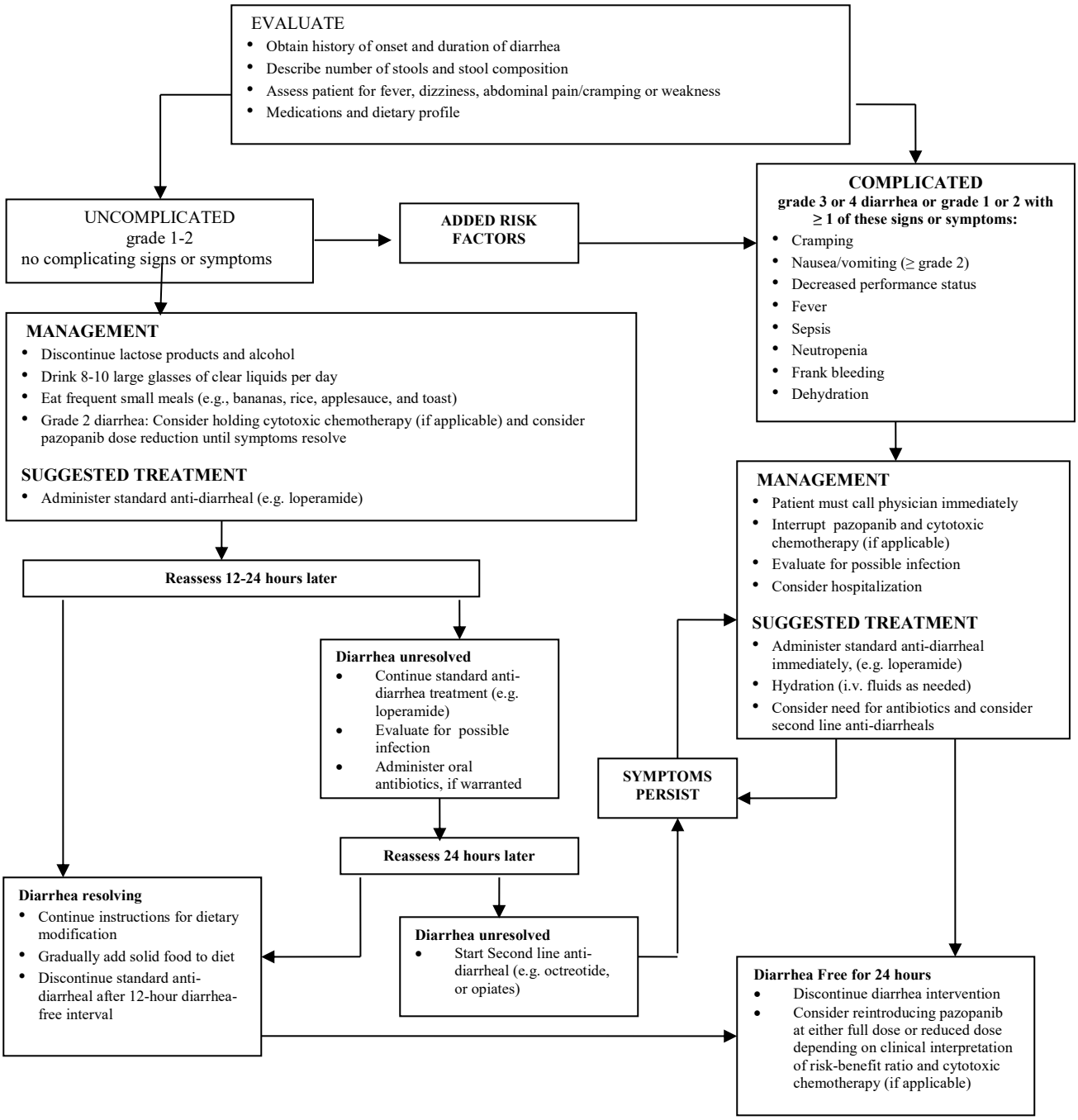
- Subjects should be educated on the signs and symptoms of diarrhea with instructions to report any changes in bowel pattern to the physician.

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

Several treatments have demonstrated efficacy in diarrhea management:

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

Figure 1. Generic flow chart for suggested management of Diarrhea



Nausea and Vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain pazopanib.
Routine pre-medication for nausea is not necessary, but symptomatic subjects should be treated with standard anti-nausea/anti-emetic therapy as necessary.
If a subject vomits after taking study medication, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists then the subject should contact their physician.

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

References:

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

Appendix IV: Blood Serum Preparation

1. Draw 10 ml whole blood into vacutainer tube(s) containing no anticoagulant.
2. Incubate in an upright position at room temperature for 30-45 min (no longer than 60 min) to allow clotting. If using a clot-activator tube, invert carefully 5-6 times to mix clot activator and blood before incubation.
3. Centrifuge for 15 min at 1000-2000 RCF. Do not use brake to stop centrifuge.
4. Carefully aspirate the supernatant (serum) at room temperature and pool into a centrifuge tube, taking care not to disturb the cell layer or transfer any cells. Use a clean pipette for each tube.
5. Inspect serum for turbidity. Turbid samples should be centrifuged and aspirated again to remove remaining insoluble matter.
6. Aliquot 1 ml of serum into each cryovial and store at –80 °C. Ensure that the cryovials are adequately labeled with the relevant information, including details of additives present in the blood.

Appendix V: Interventional Clinical Trial SAE Fax Cover Sheet – Suspected

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk [redacted]

Investigator contact details:
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

Investigator Signature	

This document contains important safety information.
If fax is received in error, please forward to [redacted]

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Appendix VI: Interventional Clinical Trial SAE Fax Cover Sheet – Not Suspected

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk [redacted]

Investigator contact details:
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

Investigator Signature	

This document contains important safety information.
If fax is received in error, please forward to [redacted]

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