Information Type: Clinical Protocol

Title:	A Phase II, Single-Arm Study of Pazopanib and Paclitaxel as First-Line Treatment for Subjects with Unresectable Stage III and Stage IV Melanoma

Compound Number: GW786034

Development Phase II

Effective Date: 29 September 2016

Repressed versions:

29 September 2016
30 Jan, 2014
15 July, 2013
18 Aug, 2010
09 Aug, 2010
1 Feb, 2010

Description:

This is a Phase II single-arm, open-label, clinical trial evaluating the efficacy and safety of pazopanib in combination with paclitaxel as first line therapy for subjects with unresectable Stage III and Stage IV melanoma. Previous cytokine therapy is permitted. Subjects must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST). Subjects who are not candidates for curative intent treatments are eligible for this study.

Treatment on study will be administered in 4-week cycles. Paclitaxel will be administered intravenously at a starting dose of 80mg/m^2 weekly for 3 weeks followed by a 1-week rest. Pazopanib will be administered orally, in a continuous regimen, with a starting dose of 800mg daily. Approximately 60 eligible subjects will be enrolled. Twenty-one subjects will be entered into the first stage of a 2-stage Simon Minimax design. If there are ≥3 responses, 39 additional subjects will be enrolled in Stage 2. The minimum number of responses required to move to the second stage, $\geq$ 3, were noted after the first 9 patients on treatment, and the study then proceeded towards the goal of accruing 60 total patients. Subjects are permitted to receive supportive care throughout the study including transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheal agents, analgesics, erythropoietin, filgramostim (Neupogen), or bisphosphonates, when appropriate. Subjects should continue treatment on study until objective disease progression is documented according to RECIST or withdrawal from the study for other reasons. Subjects discontinuing treatment with paclitaxel prior to disease progression should continue treatment with pazopanib. Subjects discontinuing both agents prior to PD will be followed for tumor assessment until PD, or until the initiation of a subsequent anti-cancer therapy in the absence of documented PD, or until death, whichever occurs first. Subjects

may continue treatment beyond the time of RECIST-defined progression at the discretion of the investigator if the subject is perceived to be experiencing clinical benefit. Overall survival will be assessed for 2 years from first study treatment.

The primary objective of the study is to evaluate the 6-month progression-free survival (6- month PFS) in this patient population. The secondary objectives are to evaluate 1- and 2- year survival, the objective response rate (ORR), clinical benefit rate (CBR), duration of response (DR) , incidence and severity of adverse events (AE), serious adverse events (SAEs) and other safety parameters. Safety and efficacy assessments will be regularly performed on all subjects. Exploratory objectives are to observe angiogenic marker modulation by the drug combination, and when possible, to identify intra-tumoral biomarkers that correlate with or are predictive of clinical response/benefit to pazopanib and to identify gene and/or protein expression in tumor tissue that may be associated with clinical outcomes or response to therapy. Other exploratory objectives, when possible, will correlate PD effects (increased diastolic blood pressure), plasma proteins (serum VEGF, soluble VEGF receptor 2, serum HIF and serum TSP1) to tumor biopsy expression levels and clinical outcome.

Subject: melanoma, pazopanib (GW786034), anti-angiogenesis

Lead Investigator/Author:

John P. Fruehauf, MD, PhD

Director Clinical Pharmacology and Developmental Therapeutics

University of California Irvine

Chao Family Comprehensive Cancer Center

101 The City Drive, Bld 55, Rm 324

Orange, CA 92868

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BP	Blood pressure
C24	Concentration at 24 hr following single-dose administration
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine Clearance
CT	Computerized tomography
CYP	Cytochrome P450 (subtypes 3A, 3A4, 2D6)
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG performance status
CRF	Electronic Case Report Form
EMEA	European Medicines Agency
EIAC	Enzyme-inducing anticonvulsants
EQ-5D	EuroQoL-5 Dimension
FDA	Food and Drug Administration
Flt-3	Fms-like tyrosine kinase-3
FKSI	FACT-Kidney Symptom Index
FU	Follow up
GCP	Good Clinical Practice
GIST	Gastrointestinal stromal tumors
GSK	GlaxoSmithKline
HIF-1α	Hypoxia-inducible factor-1α
HRT	Hormone Replacement Therapy
IC_{50}	Half-maximal inhibition
IFNα	Interferon α
IL-2	Interleukin-2
IND	Investigational New Drug
INR	International normalized ratio (anticoagulant level description)
IEC/IRB	Independent Ethic Committee /Institutional Review Board
ITT	Intend-to-treat
LD	Longest diameter
LMWH	Low Molecular Weight Heparin
MM	Metastatic Melanoma

MRI	Magnetic resonance imaging
msec	Millisecond(s)
MTD	Maximum tolerated dose
mTOR	mammalian Target of Rapamycin
MUGA	Multigated acquisition
NCI-CTC	National Cancer Institute-common toxicity criteria
OS	Overall survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PR	Partial response
PTT	Partial thromboplastin time
QD	Once daily
QTc	Corrected QT interval
RAP	Report and analysis plan
RAMOS	Registration and Medication Ordering System
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SPM	Study Procedures Manual
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
μM	Micromolar
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von Hippel-Lindau

PROTOCOL SUMMARY

Rationale

Metastatic melanoma (MM) is a devastating and incurable disease lacking effective therapies. Despite treatment options, which include palliative chemotherapy and immunotherapy, the majority of patients succumb to their disease within 6 to 9 months of diagnosis [Homsi, 2005]. Because of the lack of treatment capable of prolonging the survival for patients with MM, many patients are treated with experimental therapy on clinical trials or with supportive care.

Chemotherapy options for MM currently include dacarbazine (DTIC), temozolomide, platinum-based therapies, and taxanes. However, only DTIC is approved by the U.S Food and Drug Administration (FDA) for use in palliative treatment for MM, based on studies performed in the 1970s [Eggermont, 2004]. Despite a response rate in MM of 13%–20% [Jelic, 2002], no significant benefit in progression-free survival (PFS) or overall survival has been demonstrated with DTIC treatment. Temozolomide is an oral therapy related to DTIC that crosses the blood–brain barrier. This property may be of benefit, given the high rate of brain metastases seen in melanoma [Middleton, 2000]. Temozolomide has not been approved by the FDA for the treatment of MM, but has become the most common chemotherapy option for palliation in this disease. Taxanes, such as paclitaxel, which have been associated with a response rate in MM similar to that of DTIC, are another treatment option that has not been approved by the FDA [Gogas et al. 2004].

Combination regimens, including cisplatin, vinblastine, and DTIC (Dartmouth regimen or CVD), are associated with a higher response rate and increased toxicity compared with single-agent chemotherapy, but also lack a benefit in PFS and overall survival [Legha, 1989; Danson, 2005; Flaherty, 2006]. The combination of paclitaxel and carboplatin has moderate activity against malignant melanoma, with expected reversible hematologic toxicities. Although not prospectively compared with single agents, this combination may be a treatment option for some patients [Hodi et al. 2002]. Use of combination chemotherapy remains a treatment option that some oncologists continue to use, owing to anecdotal reports of long-term responses. An immunotherapeutic treatment, high-dose interleukin-2, is the only other approved treatment for MM. This highly toxic treatment requires regular hospitalization in a specialized intensive care unit. This treatment is associated with a response rate of 10%–20% and long-term disease-free survival (DFS) of 5% [Atkins, 2000]. However, it is also associated with a treatment morbidity rate of > 45% and a mortality rate of 2% [Atkins, 1999]. Combinations of chemotherapy and immunotherapy, referred to as bio-chemotherapy, are an alternative treatment for highly selected patients, although a large Phase III study showed higher toxicity and efficacy similar to that of single-agent chemotherapy [Atkins, 2006].

As the result of the rapid rate of progressive disease seen in patients with MM and the lack of proven therapies that change the course of the disease, MM is a disease for which a first-line experimental approach is reasonable (NCI website, http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/page9.

Angiogenesis plays a role in melanoma progression and metastasis. [Mahabeleshwar, 2007]. A phase II study of axitinib, an orally available small-molecule inhibitor of VEGFR-1, 2, and 3, in metastatic melanoma demonstrated an ORR of 19% in 32 patients Median overall survival was 6.8 months with a median progression free survival of 2.3 months [Fruehauf, 2008]. A recent study of carboplatin + paclitaxel chemotherapy combined with sorafenib biologic therapy resulted in progression-free survival (PFS) of 8.8 months (historical controls have PFS of 2−4 months) in a 100-patient, single-arm, Phase II study [Flaherty, 2006]. Bevacizumab, in combination chemotherapies including paclitaxel, has also demonstrated antitumor in metastatic melanoma. In a Phase II study evaluating carboplatin, weekly paclitaxel and bevacizumab, nine (17%) patients achieved partial remission, and another 30 (57%) achieved stable disease for at least 8 weeks. Median progression-free survival and median overall survival were 6 months and 12 months, respectively [Perez, 2009].

Pazopanib is a small-molecule inhibitor of VEGFR-1,2,3, PDGFR-B and c-KIT. [Harris, 2008] In vitro and in vivo, pazopanib has demonstrated antiangiogenic activity as well as inhibition of xenograft tumor growth. Established as tolerable, a randomized phase III trial to evaluate PFS in advanced RCC for pazopanib 800mg daily compared with placebo was initiated given a partial response (PR) rate at week 12 of 27% in a randomized discontinuation phase II trial of pazopanib in metastatic RCC. [Hutson, 2008] In melanoma, a single agent phase II study with pazopanib is planned. In light of the relevance of angiogenesis in melanoma and possible additive or synergistic benefit of other antiangiogenesis agents in combination with chemotherapy, a Phase II study of pazopanib in combination with chemotherapy in advanced stage melanoma is warranted.

Objective(s)

The primary objective of the study is to evaluate the 6-month progression-free survival (PFS) in subjects with unresectable Stage III and Stage IV melanoma.

The secondary objectives are to evaluate 1- and 2- year survival, objective response rate (ORR), clinical benefit rate (CBR), duration of response (DR) , incidence and severity of adverse events (AE), serious adverse events (SAEs) and other safety parameters. Safety and efficacy assessments will be regularly performed on all subjects.

Exploratory objectives are to observe angiogenic marker modulation by the drug combination, and when possible, to identify intra-tumoral biomarkers that correlate with or are predictive of clinical response/benefit to pazopanib and to identify gene and/or protein expression in tumor tissue that may be associated with clinical outcomes or response to therapy. Other exploratory objectives, when possible, will correlate PD effects (increased diastolic blood pressure), plasma proteins (serum VEGF, soluble VEGF receptor 2, serum HIF and serum TSP1) to tumor biopsy expression levels and clinical outcome.

Study Design

This is a Phase II single-arm, open-label, clinical trial evaluating the efficacy and safety of pazopanib in combination with paclitaxel as first line therapy for subjects with unresectable

Stage III and Stage IV melanoma. Previous cytokine therapy is permitted. Subjects must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST). Subjects who are not candidates for curative intent treatments are eligible for this study.

Approximately 60 eligible subjects will be enrolled. Twenty-one subjects will be entered into the first stage of a 2-stage Simon Minimax design [Simon, 1989]. If there are ≥3 responses, 39 additional subjects will be enrolled in this study.

The study includes a Screening/Baseline Period, a Treatment Period and a post-treatment Follow-Up Period for progression-free survival and survival. After signing the informed consent, candidate subjects will be screened against all the eligibility criteria.

All subjects will receive paclitaxel IV at 80mg/m2 and pazopanib 800mg oral daily dosing. Subjects are permitted to receive supportive care throughout the study including transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheal agents, analgesics, erythropoietin, or bisphosphonates, when appropriate. Study treatment will continue until a subject dies, or experiences disease progression, unacceptable toxicity, or withdraws consent for study participation. Dose interruptions or reductions may be required following potential drug-related toxicities. After discontinuation of study treatment, subjects will be followed until death, withdrawal of consent, or lost to follow up or until 2 years following the last subject enrolled, whichever comes first.

Study Endpoints/Assessments

Primary Endpoint

- The primary endpoint is 6-month progression free survival (6-month PFS)

Secondary Endpoints

- 1-and 2-year Survival
- Objective response rate (ORR)
- Clinical benefit response (CBR)
- Duration of response (DR)
- Incidence, severity of adverse events (AE), serious adverse events (SAEs) and other safety parameters.

Exploratory Endpoints

- Concentrations of plasma proteins (serum VEGF, soluble VEGF receptor 2, serum HIF and serum TSP1) that may be associated to angiogenesis and tumor proliferation.

- Tissue levels of angiogenic markers

1. INTRODUCTION

1.1. Background

1.1.1. Epidemiology

Melanoma accounts for approximately 5% of all cancers in the United States, with 62,480 new cases and 8,420 deaths expected to occur in 2008 with an increasing death rate since 1990. A 619% increased incidence of melanoma has been reported between 1950 and 2000, with a 165% increased mortality rate. Melanoma affects younger patients and is the second leading cause of lost productive years. It is the most common cancer in women 20 to 29 years of age. There is a slightly higher incidence in men than women, with 34,950 cases in men (5%) and 27,530 (4%) in women [SEER database, 2009]

1.1.2. Current Treatment Options for Advanced Melanoma

1.1.2.1. Chemotherapy

The prognosis for patients with advanced and metastatic melanoma classified as Stage III and IV according to the Staging System of the American Joint Committee on Cancer (AJCC) [See Section 11.1, Appendix 1], is poor with a 5-year survival rate of less than 10 percent [Jamal 2008]. Chemotherapy options for MM currently include dacarbazine (DTIC), temozolomide, platinum-based therapies, and taxanes. However, only DTIC is approved by the U.S Food and Drug Administration (FDA) for use in palliative treatment for MM, based on studies performed in the 1970s [Eggermont, 2004]. Despite a response rate in MM of 13%–20% [Jelic, 2002), no significant benefit in progression-free survival (PFS) or overall survival has been demonstrated with DTIC treatment. Temozolomide is an oral therapy related to DTIC that crosses the blood–brain barrier. This property may be of benefit, given the high rate of brain metastases seen in melanoma [Middleton, 2000]. Temozolomide has not been approved by the FDA for the treatment of MM, but has become the most common chemotherapy option for palliation in this disease. Taxanes, such as paclitaxel, which have been associated with a response rate in MM similar to that of DTIC, are another treatment option that has not been approved by the FDA [Gogas, 2004]. Combination regimens, including cisplatin, vinblastine, and DTIC (Dartmouth regimen or CVD), are associated with a higher response rate and increased toxicity compared with single-agent chemotherapy, but also lack a benefit in PFS and overall survival [Legha, 1989; Danson, 2005; Flaherty, 2006]. The combination of paclitaxel and carboplatin has moderate activity against malignant melanoma, with expected reversible hematologic toxicities. Although not prospectively compared with single agents, this combination may be a treatment option for some patients [Hodi, 2002]. Use of combination chemotherapy remains a treatment option that some oncologists continue to use, owing to anecdotal reports of long-term responses.

1.1.2.2. Immunotherapy

An immunotherapeutic treatment, high-dose interleukin-2, is the only other approved treatment for MM. This highly toxic treatment requires regular hospitalization in a specialized intensive care unit. This treatment is associated with a response rate of 10%–20% and long-term disease-free survival (DFS) of 5% [Atkins, 2000]. However, it is also associated with a treatment morbidity rate of > 45% and a mortality rate of 2% [Atkins, 1999]. Combinations of chemotherapy and immunotherapy, referred to as bio-chemotherapy, are an alternative treatment for highly selected patients, although a large Phase III study showed higher toxicity and efficacy similar to that of single-agent chemotherapy [Atkins, 2006].

As the result of the rapid rate of progressive disease seen in patients with MM and the lack of proven therapies that change the course of the disease, MM is a disease for which a first-line experimental approach is reasonable [NCI website, http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional /page9].

1.1.2.3. Anti-angiogenesis Therapy

Axitinib, a potent oral VEGFR 1,2, and 3 inhibitor demonstrated single-agent activity with an ORR of 19% in a study of 32 patients with metastatic melanoma as first or second line therapy. Additionally, an unplanned subset analysis demonstrated a survival benefit in patients with an increase in diastolic blood pressure during study therapy [Fruehauf, 2007].

In a study of 32 patients with Stage IV MM who received either bevacizumab or bevacizumab plus low-dose interferon, one patient experienced a partial response and eight patients experienced prolonged disease stabilization (24–146 weeks) [Varker, 2007]. In a Phase II study evaluating carboplatin, weekly paclitaxel and bevacizumab, nine (17%) patients achieved partial remission, and another 30 (57%) achieved stable disease for at least 8 weeks. Median progression-free survival and median overall survival were 6 months and 12 months, respectively [Perez, 2009].

A recent study of carboplatin plus paclitaxel chemotherapy combined with sorafenib biologic therapy resulted in progression-free survival (PFS) of 8.8 months (historical controls have PFS of 2−4 months) in a 100-patient, single-arm, Phase II study [Flaherty, 2006]. This study has led to two ongoing Phase III studies using the same regimen and has renewed interest in the carboplatin + paclitaxel chemotherapy regimen in this disease setting [Rao, 2006; Hodi , 2002].

1.1.3. Pazopanib: Preclinical and Clinical Experience

Pazopanib is a potent, multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR-1, -2, -3, PDGFR-α and -β and c-kit, with half-maximal inhibition (IC_{50}) values of 10, 30, 47, 71, 84 and 74 nM, respectively. It inhibits VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells (HUVEC) as well as in mouse lungs in a dose-dependent manner. Data from preclinical studies show pazopanib has significant growth inhibition of a

variety of human tumor xenografts in mice, and also inhibits basic fibroblast growth factor- (bFGF-) and VEGF-induced angiogenesis in two mouse models of angiogenesis, viz., the Matrigel™ plug assay and the cornea micropocket model [GSK Pazopanib Investigator's brochure version 7.0].

GlaxoSmithKline initiated the clinical development of pazopanib in December 2002. As of April, 2007, five Phase I, one Phase I/II, six Phase II, and one Phase III clinical studies had been initiated to evaluate the pharmacokinetics, pharmacodynamics, safety, clinical benefit, and efficacy of pazopanib alone or in combination with other compounds in patients with various types of cancer including renal cell carcinoma, ovarian, breast, multiple myeloma, and soft tissue sarcoma.

1.1.3.1. Preliminary Safety Summary

As of 09 September 2012, approximately 5000 subjects have received pazopanib as monotherapy or in combination out of approximately 7000 subjects enrolled in pazopanib oncology clinical studies. Data collected to date show that oral pazopanib is absorbed after administration and that pazopanib administration at 800 mg daily is associated with a reasonable safety profile and encouraging efficacy in various oncology settings.
In VEG105192 a randomized, double-blind, placebo-controlled Phase III study of pazopanib monotherapy in subjects with advanced RCC), the median time on treatment was approximately twice that on placebo (7.4 months versus 3.8 months) [Sternberg, 2010]. The overall frequency of AEs reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). Most common AEs reported in >20% subjects in the pazopanib arm (as of 23 May 2008) were diarrhea (52%), hypertension (40%), hair color change (depigmentation; 38%), nausea (26%), anorexia (22%), and vomiting (21%). These AEs were all reported at a higher incidence than in the placebo arm. Most of these events were Grade 1 or 2 using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) Version 3.0. More Grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The frequency of Grade 4 AE and Grade 5 event was similar between the pazopanib and placebo arms: Grade 4 in 7% and 6% respectively; Grade 5 in 4% and 3% respectively. At the time of the final overall survival (OS) analysis, a subsequent review of safety data did not reveal any changes to the previously observed safety profile; no new safety signals were detected. [Sternberg, 2013]

Based on the analysis of the safety data integrated across the 3 RCC studies VEG102616, (a Phase II study of pazopanib monotherapy in subjects with advanced RCC), VEG105192, and VEG107769 (a single arm Phase III extension

study of pazopanib monotherapy in subjects with advanced RCC) as of 09 January 2009 (N=593), the most common AEs and SAEs were similar to those observed in the pazopanib arm of VEG105192.
Study VEG108844 was a randomized, open-label, parallel group Phase III non-inferiority study to evaluate the efficacy and safety of pazopanib compared with sunitinib in subjects with advanced RCC who had not received prior systemic therapy for advanced or metastatic RCC. Approximately 876 eligible subjects (approximately 438 per treatment arm) were planned to be enrolled over the course of the study. However, due to higher than expected withdrawal rates and discordance rates between Independent Review Committee (IRC) and investigator assessments of progression, the protocol was amended to increase the number of subjects to approximately 1100 total by including all subjects enrolled in VEG108844 and VEG113078 (a substudy of VEG108844). VEG113078 was conducted in China, Korea, and Taiwan; enrolled the same subject population as VEG108844; and is almost identical in study design and conduct to allow integration of efficacy and safety data.

A total of 1102 subjects were included in the safety population (pazopanib 554 subjects; sunitinib 548 subjects). The median time on treatment was 8 months for pazopanib and 7.6 months for sunitinib. The overall frequency of AEs reported during the study was similar for each treatment group; 552 subjects (>99%) had AEs in the pazopanib arm and 544 subjects (>99%) had AEs in the sunitinib arm. However, differential safety profiles were observed between the treatment arms, with a statistically significant difference in frequencies (unadjusted for multiplicity) for many AEs. The most common AEs (>35% in either treatment arm) were diarrhea (63% in pazopanib arm, 57% in sunitinib arm), fatigue (55% in pazopanib arm, 63% in sunitinib arm), hypertension (46% in pazopanib arm, 41% in sunitinib arm), nausea (45% in pazopanib arm, 46% in sunitinib arm), decreased appetite (37% in pazopanib arm, 37% in sunitinib arm), dysgeusia (26% in pazopanib arm, 36% in sunitinib arm), and palmar-plantar erythrodysesthesia (PPE) syndrome (or hand-foot syndrome [HFS]) (29% in pazopanib arm, 50% in sunitinib arm). Of these AEs, fatigue, HFS, and dysgeusia occurred more frequently in the sunitinib arm compared with the pazopanib arm based on 95% confidence interval (CI; unadjusted for multiplicity) for relative risk excluding 1. The proportion of subjects with diarrhea and hypertension was higher in pazopanib compared with sunitinib, but the 95% CI did not exclude a relative risk of 1. The proportion of subjects with maximum Grade 3 and 4 AEs was similar between the treatment arms, with no difference in the relative risk. Grade 3 AEs of increased ALT, increased aspartate aminotransferase (AST), and headache occurred more frequently in the pazopanib arm compared with the sunitinib arm. Grade 3 AEs of fatigue,

decreased appetite, HFS, neutropenia, mucosal inflammation, thrombocytopenia, leukopenia, decreased platelet count, anemia, and decreased neutrophil count occurred more frequently in the sunitinib arm compared with the pazopanib arm. Grade 5 AEs were reported in 13 (2%) subjects in the pazopanib arm and 19 (3%) subjects in the sunitinib arm.

In VEG110727 (a randomized placebo-controlled Phase III study of pazopanib monotherapy in subjects with STS), the median time on pazopanib was 19.4 weeks, as compared with 8.1 weeks in the placebo arm. The most common AEs (≥20%) reported in the pazopanib arm (as of 23 May 2011) were fatigue (65%), diarrhea (59%), nausea (56%), weight decreased (51%), hypertension (42%), decreased appetite (40%), hair color changes (39%), vomiting (33%), tumor pain (30%), dysguesia (28%), headache (23%), musculoskeletal pain (23%), myalgia (23%), gastrointestinal (GI) pain (23%), and dyspnea (20%). Twenty-eight percent of subjects on placebo and 63% of subjects on pazopanib experienced an AE of maximum Grade 3 or higher. The proportion of subjects who experienced maximum Grade 4 and Grade 5 AEs was similar in both treatment arms.

An analysis of integrated safety data from VEG110727 and VEG20002 (a single arm Phase II study of pazopanib monotherapy in subjects with STS) showed a safety profile similar to that observed in the pazopanib arm of VEG110727 alone. Increased rates of myocardial dysfunction, venous thrombo-embolic events, and pneumothorax were newly observed in the STS studies as compared to RCC.

Rare but severe AEs previously described for VEGFR inhibitors, such as cardiac/cerebral ischemia, hemorrhage, and bowel perforation, were observed with pazopanib treatment.

The most common SAEs occurring in subjects enrolled in all pazopanib oncology studies regardless of treatment assignment include diarrhea, abdominal pain, vomiting, dyspnea,hypertension (including 1 SAE of hypertensive crisis), pyrexia, anemia, dehydration, fatigue, pneumonia, pleural effusion, neutropenia, pulmonary embolism, increased ALT, and nausea.

In study VEG105192 in subjects with RCC, the most common chemistry abnormalities, occurring almost twice as frequently on pazopanib compared with placebo included ALT (53% versus 22%), AST (52% versus 19%) and bilirubin elevations (36% versus 10%), hypophosphatemia (34% versus 11%), hypomagnesemia (26% versus 14%), hypoglycemia (17% versus 3%) and hypokalemia (9% versus 2%).

Most of these were Grade 1/2. The most common Grade 3/4 abnormalities were ALT and AST elevations. Although leukopenia, neutropenia, and thrombocytopenia were more common on pazopanib than placebo, Grade 3/4 cytopenias were uncommon.

In subjects with RCC,, the major laboratory abnormality appears to be elevation of hepatic enzymes, which typically occurred during the first 18 weeks of treatment. As of 09 January 2009, the transaminase elevations were reversible in 96 (91%) of 106 subjects with elevated ALT ≥3×ULN; 7 of the remaining 10 subjects had limited or no follow-up to determine recovery and 3 died of cancer progression with no follow-up ALT data.It was noted early in development that some of the subjects with elevated hepatic enzymes remained on study drug despite these elevations and had normalization of their transaminases while remaining on pazopanib ("adaptation"). Most subjects with transaminase elevations in whom dosing was interrupted could be successfully re-challenged.

In Study VEG108844 in subjects with RCC, the worst-case toxicity grade changes from baseline for hematologic toxicity were higher in the sunitinib arm compared with the pazopanib arm and for chemistry worst-case toxicity grade changes were similar between the pazopanib and sunitinib arms. See the investigator brochure for details.

1.1.3.2. Preliminary Efficacy Summary

Pazopanib 800mg once daily has shown efficacy and/or encouraging efficacy signals in the following settings:

- **Renal Cell Carcinoma:** In Study VEG102616, the primary analysis of the primary endpoint, progression-free survival (PFS), revealed a large and highly statistically significant improvement in PFS in the pazopanib-treated subjects compared to placebo-treated subjects (HR 0.46, 95% confidence interval [CI] 0.34 to 0.62, p<0.0000001). The median PFS in the pazopanib arm was more than double that in the placebo arm: 9.2 months (95% CI, 7.4, 12.9) versus 4.2 months (95% CI, 2.8, 4.2), respectively. The response rate (RR), defined as the percentage of subjects who achieved either a confirmed complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria was significantly higher for the pazopanib arm compared with the placebo arm by Independent Review Committee (IRC) assessment (30% vs. 3%, p<0.001). In the pazopanib arm, the median duration of response was 58.7 weeks (95% CI, 52.1 to 68.1 weeks) and the

median time to response was 11.9 weeks (95% CI, 9.4 to 12.3 weeks) by IRC assessment [Sternberg, 2010]. The median overall survival (OS) at final analysis was 22.9 months in the pazopanib arm and 20.5 months in the placebo arm. The final OS was not statistically different between the pazopanib arm and the placebo arm in (HR = 0.91, stratified log-rank p-value, 0.224). Of note, 54% of subjects in the placebo arm received pazopanib, many starting early in the study, and an additional 12% received other systemic therapies..

- Soft Tissue Sarcoma: In the VEG110727 Study, a statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm. The median PFS in the placebo arm was 7.0 weeks (95% CI: 4.4, 8.1) and in the pazopanib arm was 20.0 weeks (95% CI: 17.9, 21.3), with a corresponding HR of 0.35 (95% CI: 0.26, 0.48, $p<0.001$) as assessed by independent radiology review. The median OS at final analysis was 10.7 months in the placebo arm (95% CI: 9.0, 13.1) and 12.6 months (95% CI: 10.9, 14.9) in the pazopanib arm; HR = 0.87 (97.57% CI: 0.67, 1.13, p=0.256). In the VEG20002 Study, the rate of PFS at 12 weeks, based on investigator assessment, was 18 of 41 subjects (43.9%) for leiomyosarcoma; 18 of 37 subjects (48.6%) for synovial sarcoma; 5 of 19 (26.3%) for adipocytic sarcoma; and 16 of 41 subjects (39.0%) for other types of sarcoma

- **Ovarian cancer:** 11 of 36 subjects (31%) experienced a cancer antigen-125 (CA-125) response to pazopanib, with a median time to CA-125 response of 29 days and median duration of response of 113 days. Excluding one subject whose CA-125 decreased before she received the first dose, the biochemical response was 28% (10 subjects). Overall response rate based on modified Gynecologic Cancer Intergroup (GCIG) criteria (incorporating CA-125, Response Evaluation Criteria in Solid Tumors (RECIST), and clinical assessment) was 18% in subjects with measurable disease at baseline, and was 21% in subjects without measurable disease at baseline. Median PFS was 84 days.

- **Advanced or metastatic soft tissue sarcoma:** Rate of PFS at 12 weeks, based on investigator assessment, was 18 of 41 subjects (43.9%) for leiomyosarcoma; 18 of 37 subjects (48.6%) for synovial sarcoma; and 16 of 41 subjects (39.0%) for other types of sarcoma [Sleijfer, 2008].

- **Early-stage Non-Small Cell Lung Cancer (NSCLC):** 30 of 35 subjects (86%) experienced a reduction in tumor volume after short-term use of pazopanib median duration of 16 days) as assessed by high-resolution

computed tomography (HRCT) after preoperative pazopanib treatment [Altorki, 2008].

- **ErbB2-positive advanced or metastatic breast cancer:** A higher response rate (36.2% versus 22.2%) by independent review at Week 12 was observed in subjects on combination lapatinib 1000mg once daily + pazopanib 400mg once daily compared with lapatinib 1500mg once daily as a monotherapy, respectively (VEG20007, [Slamon, 2008c]).

- Inflammatory Breast Cancer: Investigator-assessed best ORR was numerically higher for combination lapatinib 1500 mg once daily + pazopanib 800 mg once daily compared with lapatinib 1500 mg once daily as a monotherapy [45% (90% CI: 30.9, 59.3) vs. 29% (90% CI: 17.2, 43.3)], and for combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared with lapatinib 1500 mg once daily as a monotherapy [58% (90% CI: 43.3, 71.5) vs. 47% (90% CI: 32.8, 62.1)]. However, no increase in PFS was observed compared to lapatinib alone

- Cervical cancer: There was a 34% reduction in risk for progression for subjects receiving pazopanib relative to lapatinib (hazard ratio: 0.66; 90% CI: 0.48, 0.91). The median time to investigator-assessed PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib (one-sided p=0.013)

1.1.4. Paclitaxel: Safety Summary

Paclitaxel (TAXOL®)

ADVERSE REACTIONS SIGNIFICANT—Percentages reported with single-agent therapy. Note: Myelosuppression is dose related, schedule related, and infusion-rate dependent (increased incidences with higher doses, more frequent doses, and longer infusion times) and, in general, rapidly reversible upon discontinuation.

- >10%:
  Cardiovascular: Flushing (28%), ECG abnormal (14% to 23%), edema (21%), hypotension (4% to 12%)
  Dermatologic: Alopecia (87%), rash (12%)
  Gastrointestinal: Nausea/vomiting (52%), diarrhea (38%), mucositis (17% to 35%; grades 3/4: up to 3%), stomatitis (15%; most common at doses >390mg/m^2), abdominal pain (with intraperitoneal paclitaxel)
  Hematologic: Neutropenia (78% to 98%; grade 4: 14% to 75%; onset 8-10 days, median nadir 11 days, recovery 15-21 days), leukopenia (90%; grade 4: 17%), anemia (47% to 90%; grades 3/4: 2% to 16%), thrombocytopenia (4% to 20%; grades 3/4: 1% to 7%),

bleeding (14%)
Hepatic: Alkaline phosphatase increased (22%), AST increased (19%)
Local: Injection site reaction (erythema, tenderness, skin discoloration, swelling: 13%)
Neuromuscular & skeletal: Peripheral neuropathy (42% to 70%; grades 3/4: up to 7%), arthralgia/myalgia (60%), weakness (17%)
Renal: Creatinine increased (observed in KS patients only: 18% to 34%; severe: 5% to 7%)
Miscellaneous: Hypersensitivity reaction (31% to 45%; grades 3/4: up to 2%), infection (15% to 30%)

- 1% to 10%:
  Cardiovascular: Bradycardia (3%), tachycardia (2%), hypertension (1%), rhythm abnormalities (1%), syncope (1%), venous thrombosis (1%)
  Dermatologic: Nail changes (2%)
  Hematologic: Febrile neutropenia (2%)
  Hepatic: Bilirubin increased (7%)
  Respiratory: Dyspnea (2%)

- <1% (Limited to important or life-threatening): Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity (tinnitus and hearing loss), pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances (scintillating scotomata)

- CONTRAINDICATIONS—Hypersensitivity to paclitaxel, Cremophor® EL (polyoxyethylated castor oil), or any component of the formulation

1.1.5. Preliminary Safety and Efficacy Summary- Pazopanib and Paclitaxel

Two dose-escalation phase I studies of pazopanib in combination with paclitaxel in subjects with advanced cancer have been completed.[Suttle, 2007; Tan, 2008] The first trial divided subjects into two groups, one receiving paclitaxel in combination with pazopanib, and the other receiving paclitaxel and carboplatin in combination with pazopanib.[Suttle, 2007] Paclitaxel administered D1, 8, 15 on a 28 day cycle was escalated (15-80mg/m2) with pazopanib daily starting on day 2, escalated from 400-800mg. The other group escalated every 3 week paclitaxel (80-225mg/m2) with carboplatin AUC 6 and pazopanib 800mg. Preliminary data on 9 subjects in the paclitaxel and pazopanib group yielded: grade 1/2 AEs of diarrhea, nausea, vomiting, fatigue, anorexia, dysguesia, rash, AST elevation, cough and hypertension except for one subject with grade 3

diarrhea. The pazopanib 800mg daily and paclitaxel 80mg/m2 weekly dose level was expanded given one DLT of an abscess. Six (83%) subjects demonstrated SD as the best response. Concomitant treatment with pazopanib increased paclitaxel AUC and Cmax (20-35%). The most tolerable regimen has not yet been identified.

A second trial evaluated safety and toxicity, PK and efficacy in 25 subjects with dose escalations of both weekly paclitaxel (D1, 8, and 15 on a 28 day cycle) from 15-80mg/m2 and pazopanib daily for 28 days from 400-800mg.[Tan, 2008] The optimally tolerated regimen (OTR) was defined as pazopanib 800mg daily and paclitaxel 80mg/m2 weekly. Subjects received a median of 2.5 cycles, range of 1-8. Tumor types included: breast, colon, non-small cell lung, and esophageal cancer. One DLT was seen at the OTR, a grade 3 groin abscess. Most adverse events were grade 1/2 and included: gastrointestinal toxicities (nausea/vomiting/diarrhea/constipation), systemic symptoms (fatigue/anorexia), as well as rash, alopecia, visual disturbance, and liver test elevations. Twelve of 16 subjects treated at the OTR had dose modifications, most commonly for liver test elevation; 10 subjects had dose interruptions (7) or reductions (3) of pazopanib, and 11 subjects had interruptions/delays (11) or reductions (5) of paclitaxel. Three subjects were withdrawn due to an adverse event. Again, increased AUC and Cmax of paclitaxel were observed with pazopanib. Of the sixteen subjects treated at the OTR, 5 (31%) evidenced a PR and 10 (63%) evidence SD for greater than 8 weeks.

1.2. Rationale

No therapy to date has improved overall survival in melanoma. New treatment modalities are critically important for this disease, which is the 6th leading cause of cancer in men and the 7th in women. Melanoma is a highly vascular tumor and VEGF has previously been implicated in the evolution of its pathogenesis, being directly associated with the transition from radial/horizontal to vertical growth phase. The expression of VEGF in MM is associated with a worse overall prognosis [Birck, 1999; Gorski, 2003; Lacal, 2000; Marcoval, 1997; Salven, 1997; Simonetti, 2002; Straume, 2001; Ugurel, 2001; Vlaykova, 1999].

A phase II study of axitinib, an orally available small-molecule inhibitor of VEGFR-1, 2, and 3, in metastatic melanoma demonstrated an ORR of 19% in 32 patients Median overall survival was 6.8 months with a median progression free survival of 2.3 months [Fruehauf, 2008]. A recent study of carboplatin + paclitaxel chemotherapy combined with sorafenib biologic therapy resulted in progression-free survival (PFS) of 8.8 months (historical controls have PFS of 2−4 months) in a 100-patient, single-arm, Phase II study [Flaherty, 2006]. Bevacizumab, in combination chemotherapies including paclitaxel, has also demonstrated antitumor in metastatic melanoma. In a Phase II study evaluating carboplatin, weekly paclitaxel and bevacizumab, nine (17%) patients achieved partial remission, and another 30 (57%) achieved stable disease for at least 8 weeks. Median progression-free survival and median overall survival were 6 months and 12 months, respectively [Perez, 2009].

Pazopanib is a small-molecule inhibitor of VEGFR-1,2,3, PDGFR-B and c-KIT. [Harris, 2008] In vitro and in vivo, pazopanib has demonstrated antiangiogenic activity as well as inhibition of xenograft tumor growth. Established as tolerable, a randomized phase III trial to evaluate PFS in advanced RCC for pazopanib 800mg daily compared with placebo was initiated given a partial response (PR) rate at week 12 of 27% in a randomized discontinuation phase II trial of pazopanib

in metastatic RCC. [Hutson, 2008] In melanoma, a single agent phase II study with pazopanib is planned. In light of the relevance of angiogenesis in melanoma and possible additive or synergistic benefit of other antiangiogenesis agents in combination with chemotherapy, a Phase II study of pazopanib in combination with chemotherapy in advanced stage melanoma is warranted.

2. OBJECTIVES

2.1. Primary

- To evaluate the 6-month progression-free survival (PFS) for subjects with unresectable Stage III and Stage IV melanoma.

2.2. Secondary

The secondary objectives are:

- To evaluate 1- and 2-year survival, objective response rate, clinical benefit rate (SD+PR+CR), and duration of response of subjects treated with pazopanib and paclitaxel.
- To assess safety of the combination of pazopanib and paclitaxel in this patient population.

2.3. Exploratory Objectives

- To observe angiogenic marker modulation by the drug combination.
- To identify intra-tumoral biomarkers that correlate with or are predictive of clinical response/benefit to pazopanib and to identify gene and/or protein expression in tumor tissue that may be associated with clinical outcomes or response to therapy.
- To correlate PD effects (increased diastolic blood pressure), plasma proteins (serum VEGF, soluble VEGF receptor 2, serum HIF and serum TSP1) to tumor biopsy expression levels and clinical outcome.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase II single-arm, open-label, clinical trial evaluating the efficacy and safety of pazopanib in combination with paclitaxel as first line therapy for subjects with unresectable Stage III and Stage IV melanoma. Previous cytokine therapy and immunotherapy is permitted. Subjects must have measurable disease per RECIST. Subjects who are not candidates for curative intent treatments are eligible for this study.

Approximately 60 eligible subjects will be enrolled. Twenty-one subjects will be entered into the first stage of a 2-stage Simon Minimax design. If there are ≥3 responses, 39 additional subjects will be enrolled in Stage 2.

A subject must first sign a written informed consent prior to any study related assessments or procedures. After signing the informed consent, candidate subjects will be screened against all the eligibility criteria. During the Screening/Baseline Period, a subject will be evaluated for study eligibility per protocol as defined in the inclusion/exclusion criteria [See Section 4.2 and Section 4.3]. Eligible subjects must complete all the required baseline safety assessments and disease assessments prior to enrollment and the first dose of study treatment [See Table 6 and Section 6.1 for Screening/Baseline assessments].

The study consists of a Screening/Baseline Period, Treatment Period and a post-treatment Follow-Up Period.

All subjects will be enrolled to receive pazopanib 800mg daily dosing in combination with paclitaxel. Subjects are permitted to receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheal agents, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Study treatment will continue until subjects experience disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons. During the Treatment Period, safety and disease assessments will be performed regularly according to schedules displayed in the Time and Events Table, Table 6.

Subjects who progress following study treatment may continue to receive medical treatment according to the local standard of care as per the investigator's discretion and at the subject's wish.

Subjects who withdraw from study treatment due to unacceptable toxicity will continue to have regular disease assessments until disease progression or initiation of another anti-cancer treatment(s) [See Table 6 for assessments during disease progression follow-up (FU)].

All study subjects will be followed until death due to any cause, withdrawal of consent, or until 2 years following the last subject enrolled, whichever comes first.

3.2. Discussion of Design

3.2.1. Dose Rationale for Pazopanib

Animal models (mice with human tumor xenografts and the Matrigel plug model of angiogenesis) using an osmotic pump to maintain a steady-state plasma concentration of pazopanib suggest that a concentration of >40 micromolar (μM) (>17,500ng/mL) was required for optimal *in vivo* activity. These results were further supported by studies showing that the inhibition of VEGF-stimulated receptor phosphorylation in mouse lungs also required similar plasma pazopanib concentrations for reproducible activity. The activity of pazopanib against human and mouse VEGFR-2 kinase is similar (IC_{50} of 23 and 9nM against human and mouse

VEGFR-2, respectively); therefore, similar effective concentrations are expected in humans. *In vitro* and *in vivo* results, taken together, suggest that steady-state plasma pazopanib concentrations of at least 17,500 – 22,000ng/mL (40 to 50μM) were required to optimally inhibit VEGFR-2 activity.

Evidence of biological activity associated with VEGFR inhibition was observed in cancer subjects in study VEG10003. A concentration-effect relationship was demonstrated between the plasma pazopanib concentration 24 hours after administration (C24) on Day 22 and the probability of an increase in blood pressure. The C24 at which there was a 50% probability of an in increase in blood pressure requiring a modification of antihypertensive therapy or a 15mmHg increase in mean MAP was approximately 21,000ng/mL. Preliminary DCE-MRI data indicate that doses of 800mg once daily and 300mg twice daily demonstrated effects consistent with a decrease in tumor perfusion. Mean (%CV) pazopanib C24 values were 24,800ng/mL (42.0) and 30,900ng/mL (31.5) in the 800mg once daily and 300mg twice daily dose groups, respectively. These results suggest that plasma pazopanib concentrations greater than 20,000ng/mL (46μM) maintained over the entire dosing interval are associated with biologic activity associated with VEGFR inhibition in cancer patients.

Evidence of clinical activity after pazopanib treatment with 800mg OD has been observed in patients with metastatic RCC in study VEG102616. Pazopanib doses ranging from 50mg three time weekly to 2000mg once daily (QD) were evaluated in the Phase I dose-escalation study VEG10003. Pazopanib 800mg QD dosing was relatively well tolerated and C24 concentrations were maintained above 40 μM in over 85% of patients who were treated at this dose in study VEG10003. No consistent increase in exposure was observed when the dose was increased from 800mg QD up to 2000mg QD and no maximum tolerated dose (MTD) was established in this study. Thus, a dose of pazopanib of 800mg QD was selected as the dose to be tested in this trial.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Subjects who meet all of the following inclusion/exclusion criteria will be eligible for enrollment into the study. Approximately 60 subjects will be enrolled into the study.

4.2. Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

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. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol. **Note**: It is not necessary that informed consent be obtained within the protocol-specified screening window.

2. Histologically confirmed cutaneous melanoma with 1) unresectable Stage III disease, or 2) Stage IV disease by AJCC criteria.
3. Must have measurable disease [i.e. with at least one measurable lesion, per RECIST]. A measurable lesion is defined as a lesion that can be accurately measured in at least one dimension with the longest diameter ≥20mm using conventional techniques or ≥10mm with spiral CT scan.

   Note: Subjects should be excluded if all baseline measurable lesions are within previously irradiated areas. Subjects participating in the exploratory analysis shall not have the biospied lesion(s) as the only sites of measurable disease.
4. ECOG performance status of 0 or 1 [See Section 11.2, Appendix 2 for a description]
5. Age ≥ 18 years old
6. A female is eligible to enter and participate in this study if she is of:

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

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

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

   Subjects must discontinue HRT prior to study enrollment due to the potential for inhibition of Cytochrome P450 (CYP) enzymes that metabolize estrogens and progestins [See Section 5.8]. For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female subject is determined not to be post-menopausal, they must use adequate contraception, as defined immediately below.

   Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

   - An intrauterine device with a documented failure rate of less than 1% per year.
   - Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.

- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

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

Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

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

7. Adequate organ system functions as defined in Table 1.

Table 1. Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC) Hemoglobin[1] Platelets	≥1.5 X 10^9/L ≥9 g/dL ≥100 X 10^9/L
International normalized ratio (INR)	≤1.2 X upper limit of normal (ULN)
Partial thromboplastin time (PTT)	≤1.2 X ULN
Hepatic	
Total bilirubin AST and ALT	≤1.5 X ULN ≤2.5 X ULN
Renal	
Calculated creatinine clearance[2]	≥30 mL/min
Urine Protein to Creatinine Ratio (UPC)[3]	<1

1. Subjects may not have had a transfusion within 7 days of screening assessment.
2. See Section 11.6, Appendix 6
3. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1g to be eligible.

8. Corrected serum calcium concentration within normal range per local clinical laboratory standard.

9. Left ventricular ejection fraction (LVEF) ≥lower limit of normal (LLN) as assessed by echocardiography or multigated acquisition (MUGA) scan.

4.3. Exclusion Criteria

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

1. Prior treatment with cytotoxic anti-cancer therapy. (Previous cytokine or investigational immunotherapy are permitted, but must be completed 28 days prior to first dose of study medication).
2. Prior use of other investigational or licensed tyrosine kinase inhibitors (TKIs), or agents which target VEGF or VEGF receptors (ie bevacizumab, VEGF-Trap).
3. Known history of dose-limiting hypersensitivity reactions to paclitaxel/Cremophor EL.
4. Pregnant or lactating female. Female subjects who are lactating are eligible if they discontinue nursing prior to the first dose of study drug and refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.
5. Melanoma of ocular origin.
6. History of another malignancy.

   Note: Subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated *in situ* carcinoma are eligible.
7. Life expectancy < 3 months.
8. History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis except for subjects who have previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria:
   a. Are asymptomatic

      and,

   b. Have had no clinical evidence of active CNS metastases for ≥28 days prior to enrollment

      and,

   c. Have no requirement for steroids or enzyme-inducing anticonvulsants (EIAC)
9. Clinically significant gastrointestinal abnormalities 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. Active peptic ulcer disease
   d. Inflammatory bowel disease
   e. Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
   f. History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning study treatment.

10. Presence of uncontrolled infection.
11. Prolongation of corrected QT interval (QTc) >480 milliseconds (msecs).
12. History of any one or more of the following cardiovascular conditions within the past 6 months:
    a. Cardiac angioplasty or stenting
    b. Myocardial infarction
    c. Unstable angina
    d. Symptomatic peripheral vascular disease
    e. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) [See Section 11.4, Appendix 4]
13. History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible.
14. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥150mmHg 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 on two occasions that are separated by a minimum of 24 hours. The mean SBP/DBP values from each blood pressure assessment must be ≤150 systolic and 90 diastolic mmHg in order for a subject to be eligible for the study.
15. Prior major surgery or trauma within 14 days of the first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer.
16. Evidence of active bleeding or bleeding diathesis
17. Hemoptysis within 6 weeks of first dose of study drug.
18. Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study.
19. Use of any prohibited medications within 14 days of the first dose of study medication.
20. Radiation therapy within 28 days of the first dose of study drug.
21. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity.
22. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.

4.4. Withdrawal Criteria

4.4.1. Subject Withdrawal from Study Treatment

Study treatment will continue until subjects experience disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

Subjects whose disease progresses following study treatment may continue to receive medical treatment according to the local standard of care as per the investigator's discretion and at the subject's wish.

Subjects who withdraw from study treatment due to unacceptable toxicity will continue to have regular disease assessments until disease progression or initiation of another anti-cancer treatment(s) [See Table 6 for assessments during disease progression follow-up].

4.4.2. Subject Withdrawal from Study Participation

A subject may withdraw from study participation (i.e. withdraw consent) at any time for any reason.

If a subject withdraws from study participation during the Treatment Period, the investigator must make every effort to perform all the assessments listed in the Study Treatment Discontinuation Visit in Table 6 Time and Events Table. Disease status should be assessed if not performed within the last 8 weeks.

If the subject withdraws from study participation during the progressive disease (PD) Follow-Up period, the investigator must make every effort to have the following evaluations and document the results in the CRF: disease assessments, ECOG performance status (ECOG PS) and continuation or resolution of treatment-related AEs/serious adverse events (SAEs) [see Table 6].

If the subject withdraws from study participation during the Survival Follow-Up period, the subject should be evaluated for continuation or resolution of treatment-related AEs/SAEs.

For data collection purposes, subjects are considered as completing the study if they have died during the Study Treatment or Follow-Up Periods, are lost to follow-up, or withdraw consent. If a subject has been treated or followed until death, the death certificate should be obtained, if possible, and the cause of death should be evaluated and documented.

4.5. Screen and Baseline Failures

A subject is considered to be a screen/baseline failure if the subject signs the informed consent, but withdraws before study enrollment. All potential subjects who are screened for enrollment in this study including screening/baseline failures will be listed on the Subject Screening Log/Identification List. Reasons for exclusion will be recorded for potential subjects who do not enter the study.

5. STUDY TREATMENTS

5.1. Description of Investigational Product

5.1.1. Pazopanib

The investigational product, pazopanib monohydrochloride salt (coded as GW786034B) tablets are provided as 200mg and 400mg tablets, which contain pazopanib monohydrochloride salt equivalent to 200mg and 400mg of the free base, respectively.

5.1.2. Paclitaxel

Paclitaxel used in this study will be supplied from commercial sources.

5.2. Dosage and Administration

5.2.1. Pazopanib

Pazopanib is provided as an open-label study medication. Starting on Day 1 of the Treatment Period, each subject will receive 800mg (2 X 400mg tablets) of study medication administered once daily by mouth. The 200mg tablets of study medication are provided to subjects who need dose adjustments during the study [see Section 5.3.1 for instructions on dose modification.]

Study medication should be taken without food at least one hour before or at least two hours after a meal. The time of day for administration of study medication should be relatively constant. If a subject misses a dose, the subject should take the dose as soon as possible, but not 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. In the event of vomiting at any time after taking a dose of study medication, subjects should wait until the time of the next scheduled dose to take study medication.

5.2.2. Paclitaxel

Paclitaxel will be administered intravenously as approximately 1-hour infusions weekly for 3 weeks followed by a 1-week rest period. The starting dose will be 80mg/m^2 weekly. All patients should receive pretreatment for paclitaxel infusions, with oral or IV corticosteroids, diphenhydramine or equivalent histamine H1 antagonists, and cimetidine or equivalent histamine H2 antagonists, according to standard of care. The weekly paclitaxel dose may be reduced to 65mg/m^2 for individual infusions or future cycles based on tolerability; guidelines for re-escalation to 80mg/m^2 upon recovery of toxicity are provided. Paclitaxel may be discontinued at the discretion of the investigator due to achievement of maximum benefit or tolerability.

The ideal duration of treatment cycles in this study is 4 weeks, with paclitaxel administered weekly during the first 3 weeks of each cycle, and pazopanib administered daily, continuously. In the event of paclitaxel interruption of at least one week due to reversible toxicity, a new cycle should begin, with the plan to deliver 3 consecutive weekly paclitaxel doses to prevent

unnecessary reduction in paclitaxel dose-intensity. Therefore, after each rest from paclitaxel (including those due to toxicity), a new cycle should begin, with the plan to deliver 3 consecutive weekly paclitaxel doses.

5.3. Dose Modifications for Toxicity

5.3.1. Pazopanib Dose Modifications

Dose interruptions or reductions may be required following potential drug-related toxicities. Hypertension, proteinuria, hepatotoxicity, bleeding events, vascular thrombosis, thrombocytopenia/neutropenia, and other adverse events have been reported in response to treatment with pazopanib.

At each visit during the Treatment Period, subjects should first be evaluated for the occurrence of AEs and laboratory abnormalities. Specific recommendations for management of these possible AEs along with guidelines for dose delay/modification or discontinuation of study treatment are provided in Table 2. Dose-adjustments are to be exercised whenever clinically indicated. If dose reduction is necessary, two dose reductions are permitted in a stepwise fashion (initially to 600mg and subsequently to 400mg if necessary) to achieve resolution of toxicity to grade 1 or baseline. If the toxicity does not recur or worsen, the dose can then be increased step-wise back to 600mg and 800mg after monitoring for 10-14 days at each step if toxicity does not recur or worsen.

Interruptions for more than 14 days due to toxicity or to reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), should be avoided.

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

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥150 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of ≥20 mmHg.	Step 1. Continue study treatment with 800mg dose. Step 2. Adjust current dose of or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[1] blood pressure (BP). If BP is not well-controlled within 2 weeks, follow Step 1 in scenario (B).
(B). Symptomatic, or SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1. Interrupt study treatment. 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. Restart study treatment at lower dose[2] once BP is well-controlled[1].
(C). Two or more symptomatic episodes of hypertension despite modification of antihypertensive medication(s) and reduction of study medication dose.	Discontinuation of study treatment and follow-up per protocol.
Proteinuria	
UPC <3g	Continue study treatment with 800mg per day dose. Monitor as clinically indicated.
UPC ≥3g	Step 1: Obtain a 24-hr urine protein. Step 2: If 24-hour urine protein is <3g, subject may continue treatment at 800mg/day. OR If 24-hour urine protein is ≥3g, interrupt treatment until UPC returns to <3g. Restart therapy at lower dose[2]. Monitor the subject by collecting 24-hour urine samples at the start of each 28-day treatment interval for the remainder of the overall treatment period. Step 3: If 24-hour urine protein is ≥3g following repeat dose reductions, discontinue treatment and follow-up per protocol.

AE Terms & Descriptions	Dose Modification Algorithms
Hemorrhage/Bleeding/Coagulopathy	
Grade 1	Continue study treatment with 800mg dose; monitor as clinically indicated.
Grade 2	Step 1. Interrupt study treatment until the AE resolves to ≤ Grade 1. Step 2. Restart treatment with lower dose[1]; monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥Grade 2 event after dose interruption/reduction.	Discontinuation of study treatment and follow-up per protocol. Note: If abnormality is not clearly associated with clinical consequences, contact the Lead Investigator to discuss the potential for continuation of study treatment. If agreed, subject may restart treatment at lower dose[2].
Vascular Thrombosis	
Grade 2	Continue study treatment with 800mg dose; monitor as clinically indicated.
Grade 3 or asymptomatic Grade 4	Step 1. Interrupt study treatment. Step 2. Start to treat the subject with Low Molecular Weight Heparin (LMWH). Note: Coumadin® is prohibited per protocol. Step 3. Resume study treatment at 800mg during the period of full-dose anticoagulation if all of the following criteria are met: The subject must have been treated with LMWH for at least one week. No Grade 3 or 4 hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.
Symptomatic Grade 4	Discontinuation of study treatment and follow-up per protocol.
Thrombocytopenia /Neutropenia	
Grade 1 or 2	Continue study treatment with 800mg dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2,]
Recurrent Grade 3/4 event after dose reduction	Discontinuation of study treatment and follow-up per protocol. Note: If subject is benefiting from study treatment contact the Lead Investigator to discuss course of action.
Anemia: Note no dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above	
Other Clinically Significant Adverse Events[4]	
Grade 1	Continue study treatment with 800mg dose; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt study treatment until toxicity resolves to ≤ Grade 1. Step 2. Restart study treatment at a lower dose[2]; monitor as clinically indicated[3].
Recurrent Grade 2/3, if clinically significant	Discontinuation of study treatment and follow-up per protocol.
Grade 4	Discontinuation of study treatment and follow-up per protocol. Note: If the subject is benefiting from therapy contact the Lead Investigator to discuss course of action.

1. Well-controlled BP defined as mean SBP <150mmHg and mean DBP <90mmHg.
2. Dose should be reduced by 200mg (ie 800mg to 600mg or 600mg to 400mg)
a. Adverse events are graded according to NCI Common Terminology Criteria for Adverse Events v4.0
b. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

Liver toxicity

In the event of treatment emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis, choledocholithiasis, and hepatic metastases should be investigated. Concomitant medications known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, ALT >3x ULN and concomitant bilirubin

>2.0xULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury. Table 3 provides guidelines for hepatotoxicity monitoring.

Note: As many subjects are taking multiple concurrent medications it is critical to do a thorough evaluation of the subject's concurrent medications, 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

AE Terms & Descriptions	Dose Modification Algorithms
(A). ALT of ≤3.0 x ULN	Continue study treatment at 800mg with full panel liver function tests (LFTs)[1] 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)	Continue study treatment at 800mg. Perform the following assessments for excluding hypersensitivity and other contributing factors: Eosinophil count Viral serology for hepatitis A, B and C Liver imaging Monitor subject closely for clinical signs and symptoms; perform full panel LFTs weekly or more frequently if clinically indicated until ALT/AST reduced to Grade 1. If the subject is withdrawn from study treatment, follow up per protocol.
(C). ALT >3.0 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN; **with** direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash). Or (D). ALT >8.0 x ULN **without** concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN; **with** direct bilirubin >35%) Or (E). Bilirubin elevation (defined as total bilirubin ≥3.0 x ULN) **without concomitant transaminase elevation**	Interrupt study treatment immediately Consult a hepatologist and perform the following assessments to identify co-contributing factors: Eosinophil count Viral serology for hepatitis A, B, C and E, cytomegalovirus (CMV), Epstein-Barr virus (EBV IgM antibody, or heterophile antibody, or monospot testing) Anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-mitochondrial antibody Serum creatinine phosphokinase (CPK) for possible muscle injury caused LFT elevation Liver imaging (ultrasound or CT scan) 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. No further treatment with pazopanib will be considered.

c. Full panel LFTs include: AST, ALT, alkaline phosphatase, γ-GT and total bilirubin. If at any time the total bilirubin is > 1.5 x ULN, perform bilirubin fractionation for direct and indirect bilirubin

a.

For isolated total bilirubin elevation without concurrent ALT (defined as ALT <3 X ULN), following the guideline below:

- Perform bilirubin fractionation at any time when total bilirubin is >1.5 X ULN.
- If total bilirubin is ≥2.0 X ULN and no bilirubin fractionation can be performed: dose interruption, follow up weekly with LFT until total bilirubin returned to ≤1.5 X ULN, then rechallenge.
- If total bilirubin is ≥2.0 X ULN and direct bilirubin is <35%, continue dosing at 800mg dose, perform full panel LFT weekly until total bilirubin returned to ≤1.5 X ULN.
- If total bilirubin is ≥2.0 X ULN and direct bilirubin is ≥35%: dose interruption, follow up weekly with LFT until total bili returned to ≤1.5 X ULN, discuss with before rechallenge.
- If total bilirubin is ≥3.0 x ULN, permanently discontinue dosing.

Fatigue and asthenia

Fatigue and asthenia are commonly reported symptoms in patients with cancer. Both fatigue and asthenia have been reported with pazopanib and other angiogenesis inhibitors in this class. Although the etiology of these events is generally unknown, hypothyroidism has been reported with this class of agents [Fruehauf, 2008] and may be a contributing factor in some patients with fatigue and asthenia.

To avoid any delay in the treatment of easily manageable conditions such as electrolyte disorders and to quickly recognize possible serious conditions such as cardiac dysfunction, Novartis recommends the following steps when caring for subjects with fatigue and asthenia. Subjects complaining of grade 2, 3, or 4 fatigue and/or asthenia should be investigated as appropriate including at a minimum the items outlined below.

- Subjects with grade 3 or more fatigue and/or asthenia should be seen immediately.
- A workup should include a detailed history and physical examination, measurement of serum electrolytes, liver function tests, an electrocardiogram, chest x-ray, thyroid function tests, and an early morning cortisol.
- Electrolyte abnormalities should be corrected and adrenal insufficiency or hypothyroidism should be treated with replacement therapy.
- An ACTH stimulation test should be performed if the cortisol concentration is <10mcg/dL (280nmol/L).
- If the subject's history or physical examination point towards symptoms or signs of congestive heart failure, the appropriate investigations should be performed including an echocardiogram.
- Subjects should be closely monitored on a weekly basis or more frequently if clinically indicated for duration of severe fatigue and asthenia.

Pazopanib dose and schedule should be adjusted according to dose adjustment guidelines in the protocol. Please contact the Lead Investigator or study contact if you require further guidance.

Abdominal pain

Abdominal pain is not an uncommon symptom with vascular endothelial growth factor (VEGF) receptor antagonists, of which pazopanib is one. Bowel perforations have been reported in clinical trials of pazopanib and with other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation.

Although bowel perforation is a rare event, investigators and study staff at the site are advised to be vigilant of this potential complication in subjects receiving pazopanib.

5.3.2. Paclitaxel Dose Reduction

The highest paclitaxel dose intensity possible for each subject should be maintained. In the event paclitaxel toxicity requires sustained dose reduction to 65mg/m^2, upon recovery, the paclitaxel dose may be re-escalated to 80mg/m^2 weekly at the discretion of the investigator. Subjects requiring frequent omissions or dose reductions for individual infusions (eg, one-half of administered doses during a 2-cycle period), may discontinue treatment with paclitaxel and resume therapy with pazopanib monotherapy per investigator discretion.

Hematological Toxicity

A complete blood count must be obtained prior to each paclitaxel dose. Paclitaxel dose reductions should be made according to Table 4:

Table 4. Paclitaxel Dose Reductions for Hematological Toxicity

Granulocytes*		Platelets	Paclitaxel Dose
$\geq$ 1200/mm^3	and	$\geq$ 100,000/mm^3	80mg/m^2
1000-1199/mm^3	or	75,000-99,000/mm^3	65mg/m^2 **single dose only**
< 1000/mm^3	or	< 75,000/mm^3	**Hold

* For this purpose, the terms neutrophil and granulocyte are used interchangeably.

** Hold therapy until granulocytes $\geq$ 1200/mm^3 and platelets $\geq$ 100,000/mm^3.

Paclitaxel infusions reduced to 65mg/m^2 according to the guidance in Table 4 should be followed by re-escalation to 80mg/m^2 unless the subject experiences one of the following:

- Fever ($\geq$ 38.5°C) associated with granulocytes < 1000/mm^3
- Absolute granulocyte count $\leq$ 500/mm^3 for $\geq$ 5 days
- Significant bleeding associated with a platelet count $\leq$ 40,000/mm^3
- Any platelet count $\leq$ 20,000/mm^3

In the event the above hematological toxicities are observed, the paclitaxel dose should be reduced to 65mg/m^2 for subsequent infusions after hematological recovery. No re-escalation will be allowed. If the above severe hematologic toxicities recur in subsequent cycles despite dose reduction, the subject should be evaluated for discontinuation of paclitaxel treatment. Filgramostim support is allowed.

Hepatic Toxicity

AST/ALT and total bilirubin must be obtained prior to the start of each cycle of therapy. Liver functions contributing to dose modification decisions may be the worst during the previous cycle or those observed prior to start of the next cycle. Paclitaxel dose should be modified according to Table 5 for liver function abnormalities considered to be attributable to treatment with paclitaxel or paclitaxel in combination with pazopanib.

Table 5. Paclitaxel Dose Reductions for Hepatic Toxicity

AST/ALT		Bilirubin	Paclitaxel Dose
≤ 5 x ULN	and	≤ 2.0mg/dL	80mg/m^2
5-10 x ULN	or	2.1-3.0mg/dL	65mg/m^2
> 10 x ULN	or	> 3.0mg/dL	*Hold

*Hold therapy until AST < 10 x ULN and bilirubin < 3.0mg/dL. If paclitaxel must be held for ≥ 3 weeks to allow for resolution of hepatic toxicity, the subject should be evaluated for discontinuation of paclitaxel treatment. Subjects requiring a delay in paclitaxel therapy due to hepatic toxicity should be evaluated for possible progressive hepatic disease.

Anaphylaxis/Hypersensitivity

Mild symptoms (e.g. mild flushing, rash pruritis): No treatment needed. Supervise at bedside and complete paclitaxel infusion.

Moderate symptoms (moderate flushing, rash, mild dyspnea, chest discomfort): Stop paclitaxel infusion. Administer appropriate treatment. After recovery of symptoms, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, the reaction should be reported as an adverse event and the subject should be evaluated for discontinuation of paclitaxel treatment.

Severe life-threatening symptoms (e.g. hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilators, generalized urticaria): Stop the infusion and administer appropriate treatment. Add epinephrine or bronchodilators if needed. The reaction should be reported as an adverse event and the subject should be discontinued from paclitaxel treatment.

Peripheral Neuropathy

If grade 3 toxicity develops, paclitaxel should be held until neuropathy recovers to ≤ grade 1. When treatment is resumed, the paclitaxel dose should be reduced to 65mg/m^2. If grade 3 neuropathy persists for > 3 weeks or recurs after dose reduction, the subject should be evaluated for discontinuation of paclitaxel treatment. If grade 2 toxicity develops, paclitaxel dosing should be delayed until neuropathy recovers to ≤ grade 1. Full dosing can be resumed unless the delay in therapy was > 3 weeks, in which case the paclitaxel dose should be reduced to 65mg/m^2.

Other Toxicities

If the subject develops any other grade 3 or 4 toxicity thought to be related to paclitaxel, paclitaxel should be held until symptoms resolve to grade 1 or less. When treatment is resumed, the paclitaxel dose should be reduced to 65mg/m^2. If grade 3 toxicity persists for > 3 weeks or recurs after dose reduction, the subject should be evaluated for discontinuation of paclitaxel treatment.

5.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

Votrient commercial available supply with auxiliary label will also be provided by Novartis. The study drug should be administrated and stored according to the instructions specified on the drug labels (refer to label, P I, and IB for detailed information).

5.5. Handling and Storage

Study medications will be dispatched to a site only after receipt of required documents in accordance with applicable regulatory requirements and Novartis procedures.

Study medications must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study medication, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer study medication. All study medications must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with the specific requirements for the study medications.

Study medications should be stored at room temperature up to 25°C. Study medications in unopened bottles are stable until the date indicated on the package when stored at the above condition.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

5.6. Product Accountability

The lead investigator will be responsible for study medication accountability, reconciliation, and record maintenance. In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of Novartis investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study.

After completion of the study, a final inventory of accountability records and unused study medications will be performed by the study monitor and site personnel. Unused study medications will be destroyed and proof of destruction will be forwarded to Novartis.

5.7. Treatment Compliance

A record of the number of tablets dispensed to and taken by each subject at each visit must be maintained and reconciled with the study medication and compliance records in the CRF.

The cause of any missed doses should be discussed. Any AE(s) associated with missed doses must be recorded in the CRF. Subjects should be instructed for the importance of compliance to study treatments.

5.8. Concomitant Medications and Non-Drug Therapies

5.8.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name and dates of administration are to be recorded. In addition, indication and dose information should also be captured on the CRF, if possible. If there are any questions on medications not listed below, please contact the lead investigator for further information and clarification.

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

5.8.1.1. Hematopoietic Growth Factors

Prophylactic use of hematopoietic growth factors to support neutrophil or platelet counts is permitted during this study. Filgrastim (shorter-acting G-CSF) may be administered more than 24 hours prior to the next administration of paclitaxel or no sooner than the day following the dose. Pegfilgastrim (longer-acting G-CSF) may be administered when a paclitaxel administration is not anticipated for 14 days. Treatment with pazopanib should continue during G-CSF treatment unless the subject is experiencing complicated neutropenia (prolonged or associated with fever or infection). Subjects who enter the study on stable doses of

erythropoietin or darbepoietin may continue this treatment, and subjects may start either drug during the study at the discretion of the investigator for Hgb values <10 when Fe, TIBC, and ferritin levels are within normal limits. Subjects with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

Potential Impact of Pazopanib on Other Medications

In vitro data indicate that pazopanib is a potential inhibitor for CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Pregnane X receptor transient transfection assay data suggested some potential for human CYP3A4 induction at high concentrations. However, definitive information on the metabolism and drug interaction profile of pazopanib in humans is not available.

Certain medications should be used with **CAUTION** due to the potential for alterations in the pharmacologic effects or increased adverse events secondary to the inhibition of multiple CYP enzymes by pazopanib. These medications include (but are not limited to):

- Antidepressants: amitriptyline, buproprion, fluoxetine, fluvoxamine, imipramine.
- 3-hydroxy-3-methylglutaryl (HMG) co-reductase inhibitors: atorvastatin, fluvastatin, lovastatin, simvastatin.
- Oral hypoglycemics: pioglitazone, rosiglitazone; **see below for specific recommendations on other oral hypoglycemics.**
- Benzodiazepines: alprazolam, midazolam, triazolam, clorazepate, diazepam, flurazepam.
- Calcium channel blockers: diltiazem, felodipine, nifedipine, nicardipine, nimodipine, nitrendipine, verapamil, amlodipine, nisoldipine, isradipine; **see below for specific recommendations for verapamil and diltiazem**.
- Angiotensin II blockers: losartan, irbesartan.
- Beta-blockers: carvedilol, metoprolol, propranolol, timolol.
- Anticonvulsants: phenobarbital, phenytoin, primadone, carbamazepine, oxcarbazepine.
- Miscellaneous: aprepitant, codeine, methadone, mifepristone, haloperidol, estrogens and progestins (including oral contraceptives).

Specific recommendations regarding oral hypoglycemics:

Co-administration of pazopanib with some oral hypoglycemics, including glipizide, glyburide (glibenclamide), glimepiride, nateglinide, repaglinide, gliclazide, acetohexamide, carbutamide, glibornuride, glymidine, metahexamide, and tolazamide, may result in an increase in plasma concentrations of the oral hypoglycemic agent. This increase may result in hypoglycemia. Therefore, the dose of the oral hypoglycemic agent should be reduced by 50% when pazopanib administration starts. The blood glucose should be monitored closely, and the subject should be instructed to measure their blood glucose if they experience symptoms of hypoglycemia and inform their physician if their blood glucose concentration is low. After at least 14 days of

pazopanib administration, the dose of the oral hypoglycemic agent may be increased **as necessary** to maintain adequate blood glucose control.

Specific recommendation regarding non-dihydropyridine calcium channel blockers (verapamil and diltiazem):

Co-administration of pazopanib with calcium channel blockers may result in increased plasma concentrations of the calcium channel blocker. Non-dihydropyridine calcium channel blockers, verapamil and diltiazem, have potential depressive effects on cardiac conduction and contractility. When pazopanib therapy is initiated, the administration of an anti-hypertensive or anti-anginal agent other than verapamil and diltiazem is recommended in the setting of a prolonged PR interval (greater than 200msec), sinus bradycardia (less than 60 beats per minute), or second or third degree heart block, unless the subject has a permanent pacemaker.

Potential Impact of Other Medications 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, pazopanib has been demonstrated to interact with p-glycoprotein *in vitro*. Therefore, substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with caution. These medications include (but are not limited to):

Inhibitors of CYP3A4:

- **Antibiotics:** clarithromycin, erythromycin, troleandomycin.
- **HIV:** anti-retrovirals (delaviridine), protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir).
- **Antifungals:** itraconzaole, ketoconazole, voriconazole, fluconazole.
- **Antidepressants:** nefazodone, fluvoxamine.
- **Calcium channel blockers:** diltiazem, verapamil
- **GI:** cimetidine, aprepitant.
- **Miscellaneous:** Grapefruit or its juice.

Inducers of CYP3A4:

- **Glucocorticoids:** dexamethasone.
- **Anticonvulsants:** phenytoin, carbamazepine, phenobarbital, oxcarbazepine.
- **HIV:** efavirenz, nevirapine.
- **Antibiotics:** rifampin (rifampicin), rifabutin, rifapentene.
- **Miscellaneous:** St. John’s Wort, modafinil.

5.8.2. Prohibited Medications

Co-administration of pazopanib and medications which are substrates for the CYP450 enzymes and which have the potential to cause serious and/or life-threatening adverse events is **PROHIBITED**. Prohibited medications should not be used from 14 days (or 5 half-lives, whichever time is greater) prior to the first dose of study drug until discontinuation of study drug. These medications include (but are not limited to):

- Anticoagulants: warfarin (**Note**: prophylactic low-dose warfarin is permitted)
- Oral hypoglycemics: tolbutamide, chlorpropamide
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- Neuroleptic: pimozide
- Erectile dysfunction agents: sildenafil, tadalafil, vardenafil
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexilitine, amiodarone, quinidine, propafenone,
- Immune modulators: cyclosporine, tacrolimus, sirolimus
- Miscellaneous: theophylline, quetiapine, risperidone, tacrine, clozapine, atomoxetine, tizanidine

5.8.3. Concomitant Anti-cancer Therapies

Concomitant anti-cancer treatments for melanoma with other drugs, surgical procedures or radiation therapy to sites of measurable disease are not permitted. Palliative radiotherapy outside of fields containing measurable disease is allowed. A subject's treatment with study medication should be terminated once another anti-cancer therapy has been initiated. However, the subject will be followed for survival. The new anti-cancer treatment and its start date must be recorded on the CRF.

5.9. Treatment after the End of the Study

A rollover study may be made available at the discretion of Novartis to those subjects who are exhibiting clinical benefit (stable disease or better) when all data needed to satisfy the study endpoints have been completed and collected.

5.10. Treatment of Investigational Product Overdose

No maximum tolerated dose (MTD) was reached in dose escalation studies of pazopanib administered as a single agent at doses of up to 2000mg/day. Peak pazopanib exposures occurred at 1000mg/day; similar or lower exposures were seen at doses between 1000-2000mg/day.

In the event of overdose (defined as administration of more than the protocol-specified dose), the investigator should contact the PI: John Fruehauf MD, PhD.

6. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-related assessments and procedures. The study assessments schedules and visit windows are summarized in Table 6 Time and Events Table.

Table 6. Time and Events Table

Protocol Activities	Screening	Study Treatment [1]				Post treatment	
	≤ 28 Days Prior to Enrollment	Day 1 (-3/+3) [2]	Day 8 (-3/+3)	Day 15 (-3/+3)	Day 22 (-3/+3)	End of Tx/ Withdrawal [3]	Post Tx [4]
Baseline Documentation							
Informed Consent [5]	X						
Medical/Oncological History [6]	X						
Physical Examination/ ECOG PS[7]	X	X				X	(X)
Vital Signs/Body Weight [7]	X	X	X	X		X	
Baseline Signs/Symptoms		X C1					
Laboratory Studies							
Hematology [8]	X	X	X	X		X	
Blood Chemistry including LDH [8]	X	X		X C1-2		X	
Thyroid function tests[8]	X	X (every 8 weeks)				X	
Amylase and Lipase tests [8]		X (every 8 weeks)					
UA- Urine Protein:Creatinine Ratio	X	X				X	
Pregnancy Test (as appropriate)	X (2 weeks prior to first dose)						
12-lead ECG [9]	X	X (Week 4, then every 4 weeks)				X	
MUGA scan[10]	X	X (if clinically indicated)				X	
Study Enrollment [11]	X						
Paclitaxel Infusion		X	X	X			
Pazopanib Capsule Dosing		X	→	→	→		
Disease Assessments							
Whole body PET/CT scans [12]	X	X 8-week intervals				(X)	(X)
Brain CT or MRI Scan [13]	X	X (if clinically indicated)				(X)	(X)
Other Clinical Assessments							
Adverse Events [14]	X	X	X	X	X	X	X
Pazopanib Drug Compliance [15]		X				X	
Concomitant Medications/Treatments [16]	X	X	X	X	X	X	X
Survival Follow-up [17]							X
Special Laboratory Studies							
Pharmacokinetic Plasma Sample [18]		X C1D1 (pre-dose), C2D1 and C2D28					
Soluble Proteins [19]		X C1D1 (pre-dose), C2D1 and C2D28					
Archived Tumor Tissues	X						
Fresh Tumor biopsy (when applicable) [20]	X (2 weeks prior to first dose if archived tissue is not attainable)	X C2D1					

Footnotes for Schedule of Events
1. **Study Treatment:** All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. Each cycle is 28 days in duration. Subjects discontinuing treatment with paclitaxel and continuing to receive pazopanib may have reduced clinic visits, returning to clinic at 4-week intervals. Subjects discontinuing all treatment prior to disease progression may return to clinic at 8-week intervals for disease assessments.
2. **Cycle 1 Day 1:** Hematology, blood chemistry, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of treatment with Study Medication.
3. **End of Treatment/Withdrawal:** Obtain these assessments if not completed during the previous 4 weeks on study (during the last 8 weeks on study for disease assessments).
4. **Post Treatment Follow-up:** Subjects discontinuing both agents prior to PD will be followed for tumor assessment until PD, or until the initiation of a subsequent anti-cancer therapy in the absence of documented PD, or until death, whichever occurs first. Subjects should be evaluated for safety up to 28 days after last dose of study treatment. Adverse events should be followed up until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Refer to the protocol for specific guidelines.
5. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
6. **Medical/Oncologic History and Demographics**: To include information on prior regimens for melanoma (duration of administration), description of best response observed and treatment failure.
7. **Physical Examination:** Examination of major body systems, ECOG performance status, body weight, height (at Screening visit only), and vital signs (temperature, blood pressure, heart rate, respiratory rate). Body weight to be recorded prior to each treatment with paclitaxel. Post-treatment physical examinations are for the purpose of disease assessment and safety follow-up (assessment of vital signs and body weight are not required).
8. **Hematology/Chemistry/Thyroid Testing/Amylase and Lipase:** See Table 8 for required tests. Subjects discontinuing treatment with paclitaxel and continuing to receive pazopanib may reduce hematology to 4-week intervals. Thyroid function testing (TSH, T3 and T4), amylase and lipase testing to be completed at baseline and every 8 weeks while on study therapy or as clinically indicated. Please refer to Table 10. Clinical Laboratory Parameters for specific guidance.
9. **12-lead ECG:** Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. The ECGs should be performed at the same time of the day and time matched (± 1 hour). A 12-lead ECG will be obtained at Screening/Baseline, Week 4 and then every 4 weeks during study treatment. If the mean QTc interval is prolonged (>440 msec), then the ECGs should be re-read by a cardiologist at the site for confirmation. ECGs must be completed at the time of discontinuation of each study treatment
10. **MUGA:** At baseline and during treatment as clinically indicated. A MUGA scan should be performed sooner if a subject develops signs and symptoms of CHF (ie, shortness of breath during mild exertion or when lying down, feeling very tired, cough (especially at night), swelling of the feet and/or ankles). A MUGA scan is the preferred method for LVEF measurement. If a MUGA scan cannot be performed an echocardiogram should be done
11. **Study Enrollment:** Subject number assignment will be obtained from the UCI central research office.
12. **Tumor Imaging:** Disease assessment should be performed as outlined in the assessment table, whenever disease progression is suspected, and to confirm a partial or complete response (at least 4 weeks after initial documentation of response). Disease assessment will include whole body PET/CT scans and clinical assessment of superficial disease. Assessments will be performed at screening and every 8 weeks (56 calendar days) from the enrollment date during the study. Lesions assessed by clinical methods should be recorded in the CRF. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays. The allowable window for disease assessments is +/-7 days. Imaging assessment delay to conform to treatment delay is not permitted. Subjects who discontinue study treatment due to reasons other than objective RECIST-defined PD, need to be followed every 8 weeks until PD, initiating another anti-cancer therapy or death whichever occurs first.
13. **Brain CT or MRI Scan:** Repeat brain scan required if new metastases are suspected.
14. **Adverse Events:** Subjects must be followed for adverse events from the first day of study treatment until at least 28 days after the last dose of all study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the subject provides informed consent as described in the protocol.

Footnotes for Schedule of Events
15. **Pazopanib Drug Compliance:** Pazopanib bottle(s) including any unused capsules will be returned to the clinic for drug accountability.
16. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.
17. **Post-Study Survival Status:** After discontinuation of study treatment, post-study survival status will be collected by telephone contact every 2 months until death or 2 years from first study treatment.
18. **Pharmacokinetic Plasma Samples:** (7 mL blood/sample) for pazopanib will be obtained 15 minutes prior to the morning dose (taken in the clinic) and 1 to 2 hours after that dose on the specified days. Samples will be submitted to the Fruehauf Lab for shipping.
19. **Soluble Proteins Assessment:** One 10 mL blood sample will be collected prior to dosing on the specified days.
20. **Pre-dose Fresh Tumor Biopsy**: When possible, if archived sample is not attainable, a pre-treatment sample by excisional, core or punch biopsy must be 0.5 – 1 cm^3 and collected 2 weeks prior to first dose of study therapy to allow appropriate healing time. The post-dose sample will require a pazopanib drug holiday of 2 days prior and 1 week after.

6.1. Screening and Baseline Assessments

6.1.1. Assessments within 4 Weeks of the First Dose

- Demography: date of birth, race and gender.
- Medical history: Melanoma-specific history including date of diagnosis, primary tumor type with histology/cytology determination, prior surgical and/or radiological therapies (date, organ/anatomic region(s) that have received surgical and/or radiological therapies must be documented), current stage of cancer, prior systemic treatment(s) for locally advanced/metastatic melanoma, ongoing toxicity related to prior treatment(s); history of other malignancies; other significant medical histories within the past 6 months.
- Physical examinations: height (only recorded at baseline) and body weight and current medical conditions.
- Vital signs: body temperature, blood pressure and heart rate.

  Note: If a subject presents with poorly controlled hypertension, defined as SBP ≥150mmHg or DBP ≥90mmHg, antihypertensive medication(s) should be initiated or adjusted with a goal to control the blood pressure to <150/90 mmHg. See Section 6.3.2 for instruction on blood pressure measurement and obtaining mean blood pressure values, and Section 11.5, Appendix 5 for antihypertensive medications suggested for the study.

- ECOG PS.
- Clinical laboratory assessments include hematology and coagulation tests, clinical chemistry, LDH, calculated creatinine clearance, urinalysis by UPC ratio, amylase and lipase, and thyroid function tests (TSH, T3 and T4). Clinical laboratory parameters of these tests are listed in Section 6.3.4 Table 10.
- Whole body PET/CT scan [Refer to Table 7 in Section 6.2.3 for details].
- 12-lead ECG with QTc measurement.
- MUGA or ECHO

6.1.2. Assessments within 2 Weeks of the First Dose

- Serum pregnancy test for women of childbearing potential.
- Request previous archived tumor tissue when possible.
- A punch, core, or excisional biopsy should be used to obtain approximately 0.5 – 1 cm^3 of tumor tissue when possible. The biopsied lesions may not be the only sites of measurable disease. See Section 11.8, Appendix 8 for processing instructions. Archived specimen may be used as a substitute for this pre-treatment sample. The biospiable lesion may be used as the site of the post-treatment sample.

6.1.3. Pre-dose Assessments on Day 1

- Review of the inclusion/exclusion criteria.
- Physical examination: to identify any changes in the subject's mental and medical conditions since baseline assessment that would make him/her ineligible for the study.
- Blood pressure measurements: subjects must have a blood pressure reading of <150/90mmHg to be eligible. If a subject has been treated with anti-hypertensive medications during the Baseline Period, the blood pressure must be re-assessed on two occasions consecutively that are separated by a minimum of 24 hours. The mean SBP/DBP values from both blood pressure assessments must be <150/90mmHg in order for a subject to be eligible. These two assessments must also be the most recent ones prior to enrollment (the blood pressure values from the later assessment will be used as the subject's baseline blood pressure values). All the blood pressure readings must be recorded on the appropriate CRF. See Section 6.3.2 for instruction on blood pressure measurement and obtaining mean blood pressure values.
- ECOG PS: Any changes since baseline assessment should be recorded in the CRF. Subjects having deterioration of ECOG PS to ≥2 will be excluded from the study.
- Review results of all the other baseline assessments to determine the subject's eligibility for the study. Any screening laboratory results result outside the normal range will be repeated (prior to the first dose) at the discretion of the Principal Investigator. All laboratory results must be within the values outlined in Section 4.2, Inclusion Criteria before the first dose of study drug.
- Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.
- Obtain a blood plasma sample for proteomics research.
- Obtain a blood plasma sample for pharmacokinetics research.

6.2. Efficacy

6.2.1. Primary Endpoint

- The primary endpoint is 6-month progression free survival (6-month PFS)

6.2.2. Secondary Endpoints

- 1-and 2-year Survival
- Objective response rate (ORR)
- Clinical benefit response (CBR)
- Duration of response (DR)

- Incidence, severity of adverse events (AE), serious adverse events (SAEs) and other safety parameters.

Exploratory Endpoints

- Concentrations of plasma proteins (serum VEGF, soluble VEGF receptor 2, serum HIF and serum TSP1) that may be associated to angiogenesis and tumor proliferation.
- Tissue levels of angiogenic markers, including p53, HIF, CD31, nNOS, TSP1, and VEGF
- BRAF mutation status
- In vitro response of tumor cells grown in culture with vascular endothelial cells to pazopanib, paclitaxel, topotecan and resveratrol.

6.2.3. Methods, Scope and Schedules of Disease Assessments

The following methods are acceptable for disease assessments in this study. The disease assessment scope and schedules are summarized in Table 7.

Whole body PET/CT scans: Dual-modality PET/CT imaging should be performed using a biograph (Siemens Medical Solutions, Hoffman Estates, Ill) or equivalent which provides separate CT and PET data sets, which can be accurately fused on a computer workstation.

Note: chest X-ray is not acceptable for assessing measurable lesions.

Table 7. Disease Assessment Scope and Schedules

Anatomic Region & Assessment Modality[1,2]	Baseline[3]	Following First Dose[4]
Whole body PET-CT scans	To be performed on all subjects.	To be performed on all subjects every 8 weeks from date of first dose (+/- 7 days).
Head CT or MRI	To be performed on all subjects. **Note:** subjects with a positive scan must be excluded from the study[5]	To be performed only on subjects if clinically indicated.

d. The following information must be documented: date of assessment, diagnostic technology used for each anatomic region, description of the type and site of a lesion (e.g. liver mass).
e. The same method, technique should be used to characterize each identified lesion at baseline and subsequent disease assessments.
f. All the baseline disease assessments should be completed within 28 days prior to enrollment.
g. Disease assessments should be performed at the indicated frequency following the first dose until documented disease progression, death or upon initiating another anti-cancer treatment, whichever occurs first.
h. Subjects who have previously-treated CNS metastases (surgery ±radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria are eligible: 1) are asymptomatic, 2) have had no evidence of active CNS metastases for ≥28 days prior to enrollment, and 3) have no requirement for steroids or EIACs

6.2.3.1. Measurability of Tumor Lesions at Baseline

All measurements should be recorded in metric notation, using a ruler or calipers. All identified tumor lesions are to be classified as measurable or non-measurable per RECIST criteria.

Measurable lesions: lesions that can be accurately measured in at least one dimension with the longest diameter ≥20mm using conventional techniques, or ≥10mm with spiral CT scan.

Non-measurable lesions: all other lesions, including lesions too small to be considered measurable (longest diameter <20mm using conventional techniques or <10mm with spiral CT scan), and the following lesions and disease sites: bone lesions, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, and cystic lesions.

Measurable disease: subjects presenting with at least one measurable lesion at baseline are identified as having **measurable disease.** Only subjects with baseline measurable disease are eligible for the study. If the **measurable disease** is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology/histology evaluation.

Subjects presenting with the following baseline conditions must be excluded from the study: 1) positive head CT or MRI scan for CNS metastasis (except as noted in Table 7); 2) all measurable lesions are within previously irradiated areas.

6.2.3.2. Determination of Target and non-Target Lesions

At baseline, all the lesions must also be categorized as "Target" or "non-Target" lesions using the following RECIST guideline.

Target lesions: all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions,*** and measured and recorded at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Lesions that are present within a previously irradiated area cannot be selected as target lesions.

Non-target lesions: all other lesions (or sites of disease) should be identified as non-target lesions, and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout subsequent assessments.

6.2.3.3. Response Evaluation of Measurable Disease

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. During Treatment Assessments, any new lesion(s) must be recorded in the CRF. If the lesion(s) noted at baseline is not evaluated at the subsequent Treatment Assessment, this will be noted as 'not done' (ND) in the CRF.

Response criteria for target and non-target lesion(s) are presented in Table 8.

Table 8. Response Criteria for Target and non-Target Lesions

Evaluation of Target Lesions	
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD
Progressive disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Not evaluable (NE)	Any subject who cannot be classified by one of the four preceding definitions
Evaluation of non-Target Lesions	
Complete response (CR)	The disappearance of all non-target lesions
Incomplete response/Stable Disease (SD)	The persistence of one or more non-target lesion(s)
Progressive disease (PD)	The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Note: New bone scan lesions that are equivocal may be confirmed using X-ray, CT or MRI.

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

Table 9 shows the overall response for all possible combinations of tumor responses in target and non-target lesions, with or without the appearance of new lesions.

Table 9. Evaluation of Best Overall Response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue on radiographic evaluation. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

6.2.3.4. Evaluation of Disease Progression

During the course of the study, the investigator will assess a subject's disease status based on the radiological assessment (as below) and clinical assessment, and will make clinical decisions on the subject's care based on medical judgment. Disease assessments by the investigator at baseline and subsequent visits must be documented in the source records and case report forms.

The primary method for assessing disease progression will be based on radiologic assessments using the methods described in Section 6.2.3. The primary method for assessing disease progression will be based on radiologic assessments using the methods described in Section 6.2.3.1. Every effort should be made to have a radiological assessment to objectively confirm progression in subjects who experience progression based only on the subject's overall deterioration of health status. However it is anticipated that some subjects will have symptomatic progression that cannot be confirmed by radiologic assessment. If a subject experiences symptomatic progression at a certain time point that meets all of the following three criteria with proper documentation, the subject is considered to have progressive disease. Thus, symptomatic progression is defined as meeting all three criteria: (1) ECOG performance status of at least 3, (2) subject is unable to have follow-up radiologic assessment due to performance status decline, and (3) symptomatic decline deemed to be related to metastatic disease (not toxicity from therapy or concurrent illness.)

6.2.3.5. Survival Assessment

All subjects should be followed up to two years from date of enrollment or until death whichever occurs first, if possible. The date of death and cause of death should be evaluated and documented in the appropriate CRF.

6.3. Safety

A secondary objective of this study is to evaluate and compare the incidence and severity of adverse events (AE), serious adverse events (SAEs) and other safety parameters.

6.3.1. Physical Examination

Physical examination is assessed at Screening/Baseline, pre-dose on Day 1, and every 4 weeks thereafter until discontinuation of study treatment. Physical examination includes height (baseline only), body weight and evaluation of the subject's medical conditions. Any new or worsening of medical conditions from the baseline condition (pre-dose on Day 1) should be recorded in the AE or SAE CRF.

6.3.2. Vital Signs and Blood Pressure Monitoring

Vital signs, including heart rate, temperature, and blood pressure should be obtained at Screening/Baseline, pre-dose on Day 1, Day 8 and Day 15 of every combination cycle until discontinuation of study treatment.

As hypertension is a common drug-related AE observed from other pazopanib studies, blood pressure monitoring is mandatory. The following instructions should be followed for cuff measurement of blood pressure:

Sitting blood pressure should be measured after the subject has been sitting quietly for at least 10 minutes. The same cuff method should be used to measure blood pressure throughout the study. All measurements will be made on the same arm using the same cuff size and the same equipment. Diastolic blood pressure will be measured at the disappearance of Korotkoff sounds - phase V. If possible, measurements will be taken by the same staff member at each visit.

At each visit, blood pressure should be measured three times at approximately 2-minute intervals. All three blood pressure values should be recorded on the CRF. These three values should be averaged to obtain mean diastolic blood pressure, and mean systolic blood pressure. The mean diastolic and the mean systolic blood pressures are to be used to determine if the subject's blood pressure is within the well-controlled range; or if the subject needs medical attention. Refer to Section 5.3.1 for the algorithm of dose modification of study medication in event hypertension occurs; refer to Section 11.5, Appendix 5 for recommendations for management of hypertension during the study treatment.

6.3.3. ECOG PS

ECOG PS is assessed at Screening/Baseline, pre-dose on Day 1 and every 4 weeks thereafter until discontinuation of study treatment. If subjects discontinue study treatment without disease progression (e.g., withdrawal study treatment due to unacceptable toxicity), continue the assessments of ECOG PS every 8 weeks in accordance with the disease assessments until subjects experience disease progression.

6.3.4. Clinical Laboratory Assessments

Hematology should be performed at Screening/Baseline and prior to each paclitaxel infusion on Day(s) 1, 8, 15 of each cycle. If subjects discontinue paclitaxel study treatment and continue on pazopanib monotherapy, hematology should be performed every 4 weeks.

Clinical chemistry, liver function tests (ALT and AST) and coagulation should be performed at Screening/Baseline and every 2 weeks for the first 2 cycles, then every 4 thereafter until discontinuation of study treatment.

Coagulation tests should be performed at Screening/Baseline and every 4 weeks thereafter until discontinuation of study treatment.

Amylase and lipase tests should be performed at Screening/Baseline and every 8 weeks following the first dose until discontinuation of study treatment.

Urinalysis by urine protein:creatinine ratio should be performed at Screening/Baseline and every 4 weeks thereafter until discontinuation of study treatment. Refer to Section 11.6, Appendix 6 for reference for UPC calculation.

The thyroid function tests should be performed at Screening/Baseline and every 8 weeks following the first dose until discontinuation of study treatment. Serum thyroid-stimulating hormone (TSH), total serum T4, and triiodothyronine (T3) resin uptake will be assessed.

Table 10. Clinical Laboratory Parameters

Clinical Chemistry	Alkaline phosphatase, Bilirubin (total)[1], Blood Urea Nitrogen (BUN), Creatinine[2], Calcium, Potassium, Sodium, Glucose, Lactate Dehydrogenase (LDH), Protein (total), Magnesium and Inorganic phosphate
Liver Function Tests (LFTs)	Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)
Pancreatic Function Tests	Amylase and Lipase
Hematology	Hematocrit (HCT), Hemoglobin (HGB), Platelet count, White Blood Cell (WBC) count, Neutrophil count (ANC), Eosinophil count, and Lymphocyte count
Coagulation Tests	International Normalization Ratio (INR) and Partial thromboplastin time (PTT)
Urinalysis	Urine protein creatinine ratio (UPC)
Thyroid Function Test	TSH, free T4, free T3

i. If total bilirubin ≥1.5 ULN, direct and indirect bilirubin will be measured
j. Estimated Creatinine Clearance (CrCl) is calculated at Baseline using Cockcroft and Gault formula

6.3.5. 12-Lead Electrocardiogram

There is no preclinical or clinical evidence of an effect on QTc with either pazopanib or lapatinib. However, 12-lead ECG will be obtained at Screening/Baseline, Week 4 and every 4 weeks during the Treatment Period for QTc monitoring. Prior to each ECG test, the subject should be at rest for approximately 10 minutes. The subject should be in the semi-recumbent or supine position; the same position must be used for all subsequent ECG tests.

All ECGs must include QTc measurements either manually or machine calculated using Bazett's formula, and recorded in the CRF. The Bazett's formula is:

$QTcB = QT / RR^{1/2}$

At Screening/Baseline, if QTc interval is > 480 msecs, subject will be excluded from the study.

If a QTc ≥ 440 msec is noted on a scheduled or unscheduled ECG, then 2 additional ECGs should be obtained within 5 minutes to confirm the abnormality. The average QTc

will be determined from the 3 ECG tracings by manual evaluation and will be used to determine continued eligibility. If the average QTc is less < 430 msec, the subject may continue therapy. If the average QTc is ≥ 430 msec, the study treatment should be discontinued immediately.

The subject should be treated appropriately for QTc prolongation and monitored until resolution is documented by a repeat ECG with QTc intervals returning to < 430 msec. No further therapy will be allowed.

6.3.6. Pregnancy Test

A screening serum β-HCG pregnancy test is mandatory for all women of child-bearing potential and should be done within 2 weeks prior to the first dose of study medication. Thereafter, the serum pregnancy test only needs to be repeated if clinically indicated or as required by local regulation.

6.3.7. Safety Assessments upon Discontinuation of Study Treatment

Subjects should have the following safety assessments upon discontinuation of study treatment: physical examination and vital signs, ECOG PS, LFTs, clinical chemistry and, hematology and coagulation tests, urinalysis, thyroid function tests (the above assessments can be omitted if the last assessments are performed within 6 weeks of the previous assessments), and ECG (this assessment can be omitted if the last assessments are performed within 12 weeks of the previous assessments). The date and reason for discontinuation of study treatment must be recorded clearly in the Study Treatment Discontinuation CRF.

6.3.8. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.3.8.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Examples of an AE **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Examples of an AE **does not include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy). Note, the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For Novartis clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

6.3.8.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria,

the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All grade 4 laboratory abnormalities

6.3.9. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., ECGs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

6.3.10. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (e.g., disease progression) does not need to be reported as an SAE. Progression of the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death due to progressive disease is to be recorded on the 'Record of Death' CRF page and not as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between study treatment (pazopanib) or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

6.3.11. Time Period, and Frequency of Detecting AEs and SAEs

All SAEs that are identified from the time a subject consents to participate in the study until he or she has completed the study and that are assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or as related to a Novartis concomitant medication must be reported promptly to Novartis. Refer to Section 6.3.13, Prompt Reporting of Serious Adverse Events and Other Events to Novartis, for guidance on reporting of SAEs.

In addition, **all** AEs and SAEs will be collected and recorded from receipt of first dose of study drug until 28 days have elapsed following cessation of study drug, regardless of initiation of a new cancer therapy or transfer to hospice.

The investigator will monitor all AEs/SAEs that are ongoing after discontinuation of study drug until resolution, until the condition stabilizes, or until the subject is lost to follow-up

6.3.12. Pregnancy

6.3.12.1. Time period for collecting pregnancy information

The time period for collecting pregnancy information is identical to the time period for collecting AEs, as stated in Section 6.3.11 “Time Period, Frequency, and Method of Detecting AEs and SAEs”, from first dose of study treatment to 28 days after last dose.

6.3.12.2. Action to be taken if pregnancy occurs

If a female subject becomes pregnant while participating in the study, the study treatment must be immediately terminated. The investigator will collect pregnancy information record on the appropriate form and submit it to Novartis within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE [see Section 6.3.8, of the protocol for definitions of AEs/SAEs and a description of follow-up].

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the investigational product by the investigator, will be reported to Novartis as described in Section 6.3.13. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

6.3.12.3. Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study and record the pregnancy information on the appropriate form and submit it to Novartis within 2 weeks of learning of the partner's pregnancy. The partner will also be followed for the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications, and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis.

6.3.13. Prompt Reporting of SAEs to Novartis

SAEs will be reported promptly to Novartis as described in the following table once the investigator determines that the event meets the protocol definition for that event.

6.3.13.1. Timeframes for Submitting SAE Reports to Novartis

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 investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

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 to (fax: 877-778-9739) within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets.**

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of pazopanib and considered by the investigator to be related or possibly related to pazopanib must be reported to Novartis 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.

6.3.13.2. AE and SAE Documentation and Follow-up Procedures

The investigator will review and adhere to the following procedures:

- Method of Detecting AEs and SAEs
- Recording of AEs and SAEs
- Evaluating of AEs and SAEs
- Completion and Transmission of SAE Reports to Novartis
- Follow-up of AEs and SAEs
- Post-study AEs and SAEs
- Regulatory Reporting Requirements for SAEs

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to Novartis are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4. Biomarker(s)

6.5. Biomarker Research

Plasma/Serum Biomarkers

Approximately 10ml of blood will be taken from subjects for preparation of plasma for biomarker research at the timepoints specified in Table 6. Examination of pre-dose protein profiles may uncover novel blood-borne protein candidate biomarkers profiles

which could be used to predict drug response. In particular, circulating levels of solubleVEGF ligand, soluble VEGF receptor 2, serum HIF and serum TSP1 will be investigated. Analyses will be carried out at the UCI Fruehauf laboratory.

The plasma samples will be "coded" with a study specific number that can only be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number) therefore the true identify of the subject will remain unknown to anyone outside of the study investigator or site staff.

Samples will be retained for a maximum of 15 years after the last subject completes the trial.

Instructions on sample preparation, storage are provided in Section 11.7, Appendix 7.

Archived Tumor Biomarkers

Archived formalin-fixed paraffin embedded tumor tissue from the time of original diagnosis (or from second surgery for metastatic disease) will be tested to determine intra-tumoral expression levels of relevant biomarkers (encoded in RNA or protein) in the angiogenesis pathway (e.g. VEGFR, c-kit) and potentially other biomarkers that are downstream or related to these pathways. In addition, analyses of underlying genetic aberrations (mutations, amplifications, and deletions) will be performed in DNA isolated from the tumor tissue. Biomarkers will be analyzed using appropriate technologies such as immunohistochemistry and transcriptional profiling.

Preferably a tumor block or a minimum of fifteen (20) slides of paraffin-embedded tissue from the tumor obtained at the initial diagnosis or recent biopsy or surgery (archived tumor tissue) should be sent for testing. Biomarker analyses will be carried out at the UCI Fruehauf laboratory. BRAF mutation status will be tested at an outside laboratory on tissue sections.

Fresh Tumor Biomarkers

To test the hypothesis that tissue levels of angiogenic markers are modulated by the drug combination, IHC assays for HIF, p53, TSP1, VEGF and vessel counts (CD31) on pre-treatment tissue sections and on post-treatment biopsies from consented subjects with subcutaneous lesions when possible will be performed. Archived formalin-fixed paraffin embedded tumor tissue from the time of original diagnosis (or from second surgery for metastatic disease) may also be used to substitute the pre-treatment tissue samples. Analyses will be carried out at the UCI Fruehauf laboratory. Tumor biopsy specimens will be grown in co-culture with vascular endothelial cells and exposed to pazopanib alone and in combination with paclitaxel, topotecan and resveratrol to determine the effects of different tumor samples on endothelial cell response. Gene arrays will be performed on the tumor and endothelial cells to determine if a gene signature is associated with sensitivity or resistance to pazopanib.

7. DATA MANAGEMENT

For this study, subject data will be collected in the subject's source documents and entered onto UCI generated case report forms (CRFs). The UCI central research office will be responsible for data management.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The goal of this single arm, open label, phase II study is to determine if paclitaxel and pazopanib demonstrate clinically significant activity as reflected by the proportion of subjects alive without progression six months after the start of treatment, or alternatively, if the level of activity is clinically irrelevant. Based on data from a meta-analysis of trials in stage IV melanoma [Korn, 2008], the sample size for this study is determined on the assumptions that the 6 month PFS of 30% or greater for subjects receiving pazopanib/paclitaxel in the first-line treatment setting will be of significant interest for further evaluation. If the 6-month PFS probability is less than 15%, further evaluation of this combination in this patient population will not be of interest. If 13 or more subjects survive and are free of disease progression beyond six months, this combination therapy will warrant further evaluation in this patient population. This design has a significance level of 6% (probability of falsely declaring an agent with a 15% six-month PFS rate to warrant further study) and a power of 88% (correctly declaring an agent with a 30% six-month PFS rate as warranting further study).

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

A total of 60 subjects will be enrolled to obtain a minimum of 55 fully evaluable subjects for a sufficient estimate of the 6-month PFS probability, the 6-month overall survival probability and toxicity rates to within +/-13% (95% confidence interval). Assuming that at least 80% of 55 eligible subjects have measurable disease, this would be sufficient to estimate the response probability to within +/- 15% (95% confidence interval). Any toxicity occurring with at least 5% probability is likely to be seen at least once (94% probability).

8.2.2. Analysis Populations

The Intent-to-Treat (ITT) population will comprise all randomized subjects and will be used for the analysis of efficacy data.

The Safety population will comprise all randomized subjects who receive at least one dose of investigational product, and will be based on the actual treatment received if this differs from that to which the subject was randomized. The safety population will be used for the analysis of safety data.

8.2.3. Analysis Data Sets

The primary data set for assessing efficacy will comprise the intent-to-treat population. The primary data set for assessing safety will comprise the safety population defined in Section 8.2.2 Analysis Populations.

8.2.4. Early Stopping Rule

The purpose of implementing a Simon 2-stage Minimax design is to minimize the number of subjects exposed to pazopanib when unfavorable results occur [Simon, 1989]. For the Simon two-stage design, and with a Type I error rate (alpha) of 0.05, power of 90%, a null proportion of 0.10 and an alternative proportion of 0.25, the total sample size is 66. The first stage is n1=21 with a decision rule to stop for futility if there are 2 or fewer responses.

8.2.5. Key Elements of Analysis Plan

Withdrawal

Subjects will be treated until disease progression or withdrawal from study due to unacceptable toxicity. Subjects may also withdraw from the study for other reasons prior to disease progression or unacceptable toxicity. All subjects who withdraw from the study will be included in analyses up to the time of withdrawal, regardless of the duration of treatment.

Missing Data

As the period of treatment for any subject will be dependent on its efficacy and toxicity, the duration of follow-up will vary between subjects. Consequently, there will be no imputation for missing data. Where appropriate, available data will be summarized over specified intervals (e.g. from enrollment until withdrawal from the study) using suitable summary statistics.

For the PFS endpoint, the date associated with the last visit with adequate assessment will be used for those subjects who are alive and have not progressed at the time of analysis; such subjects will be considered censored in the analysis. If a progression event occurs after an extensive lost-to-follow-up time (12 weeks or greater) the primary analysis will censor those subjects at the date of their last visit with an adequate assessment.

Derived and Transformed Data

Details of the determination of overall tumor response (complete response, partial response, stable disease, or progressive disease) are given in Section 6.2.3.3 “Response Evaluation of Measurable Disease”.

Table 11 represents how progression and censoring dates are assigned in the primary analysis. The primary method for assessing progression will be based on radiologic

assessment. However it is anticipated that some subjects will have evidence of clinical progression prior to radiological progression.

Table 11. Assignments for Progression and Censoring Dates

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Enrollment	Censored
Progression documented at or between scheduled visits (during adequate follow-up)[1]	Date of scan	Progressed
No Progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Study withdrawal for toxicity or other reason(prior to documentation of progression or death)	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of Death	Progressed
Death prior to progression during adequate follow-up	Date of Death	Progressed
Death or progression after an extended lost-to-follow-up time (greater than 12 weeks)	Date of last visit with adequate assessment	Censored

b. The subject need not be on IP at the time of the scan. In this situation, it is possible that the subject has discontinued IP.

k.

An adequate disease assessment comprises imaging assessment of the target tumor lesion(s) and non-target tumor lesion(s)/site(s) using CT and/or MRI of the chest, abdomen and pelvis with a schedule of every 8 weeks. A subject may have a bone scan to confirm a CR/PR. Subsequent bone scans will be performed as clinically indicated.

New bone scan lesions that are equivocal will be considered as new malignant lesions if a confirmatory assessment using X-ray, CT or MRI is not available, and the subject will be determined as having progressive disease.

If a bone assessment is missing at baseline, any new bone lesions identified after the first dose that is either consistent with or equivocal for tumor metastasis will be considered as new bone (malignant) lesions and the subject will be considered as having progressive disease.

Other Issues

Data from all participating centers (if applicable) will be pooled prior to analysis.

A summary and listing of protocol violations will be provided.

Demographic and baseline characteristics will be summarized.

Any deviations from, or additions to, the original analysis plan described in this protocol will be documented.

8.2.5.1. Efficacy Analyses

8.2.5.1.1. Primary Analysis

6-month Progression-free Survival (PFS)

This is defined as the percentage of subjects who are free of RECIST-defined objective disease progression at 6 months after study treatment start.

Subjects in the ITT population who discontinue the study prior to 6 months will be included in the denominator when calculating the percentage.

8.2.5.1.2. Secondary Analyses

Objective Tumor Response Rate

This is defined as the percentage of subjects achieving either a complete or partial tumor response per RECIST criteria. The response rate will be calculated from the review of best response which records confirmed cases of PR and CR only. Confirmation will occur at least 4 weeks after the initial response. Stable disease (SD) will also be defined by 8 weeks or greater and will be summarized by less than 6 months vs. equal or greater than 6 months.

Subjects in the ITT population with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage.

Clinical Benefit Response

This is defined as the percentage of subjects achieving either a complete, partial tumor or stable disease response per RECIST criteria. Confirmation will occur at least 4 weeks after the initial response for partial and complete responders. Stable disease (SD) will also be defined by 8 weeks or greater.

Subjects in the ITT population with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage.

Duration of Response

Duration of response analyses will be restricted to the subgroup of the population who experience a response during the study. Duration of response will be defined as the time from first documented evidence of response (CR/PR) until the first documented sign of disease progression or death, if sooner.

For subjects who do not progress or die, duration of response will be censored on the date of last assessment.

Duration of response will be summarized using a Kaplan-Meier methods and displayed graphically where appropriate.

One and 2- year Survival

This is defined as the percentage of subjects who are alive at 1 year and 2 years after enrollment. For subjects who do not die, time to death will be censored at the time of last contact.

8.2.5.2. Safety Analyses

The safety population will be used for the analysis of safety data.

Extent of Exposure

The number of subjects who receive investigational product will be summarized according to the duration of therapy.

Adverse Events

AE rates and changes in laboratory results will be summarized in tabular form.

AEs and toxicities will be graded according to the National Cancer Institute-common toxicity criteria (NCI-CTC), Version 4.0. Summaries of the number of toxicity grades for both laboratory and non-laboratory data will be presented. If the AE is listed in the NCI-CTC, the maximum grade will be summarized. Otherwise, the maximum intensity will be summarized.

AEs will be coded using the standard dictionary (MedDRA), and grouped by system organ class. They will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, for drug-related AEs, for SAEs, and for AEs leading to withdrawal from the study treatment.

The incidence of deaths will also be reported.

Clinical Laboratory Evaluations

Hematology, coagulation parameters, clinical chemistry, and urinalysis data will be summarized at each scheduled assessment. Hematology, coagulation parameters and clinical chemistry will be summarized by NCI-CTC version 4.0 and by data outside the reference range for each scheduled assessment.

Other Safety Measures

Vital signs (blood pressure, heart rate, temperature, and weight) will be listed for each subject and change from baseline will be included for blood pressure and heart rate. A

descriptive summary including change from baseline pre-dose will also be presented. Individual profiles of blood pressure will be plotted by time.

All ECG parameters including the corrected QT interval (QTc) will be listed for each subject and summarized at each scheduled assessment time. Change from baseline will be summarized and an analysis of central tendency (means, medians) will be presented. A categorical analysis for each QTc parameter will be performed to determine the number of subjects at each time point for the following categories:

- QTc. <400, 400 to <440, 440 to 450, and >450 msec.
- QTc change from baseline. 30 to <60 msec. and ≥60 msec.,

8.2.5.3. Biomarker(s) Analyses

The results of biomarker investigations will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Relationships between baseline patient characteristics, biomarkers and outcome variables will be explored with appropriate techniques.

A preplanned analysis of hypertension (HTN) as a PD marker will also be carried out to determine if this is a surrogate of efficacy. BP will be determined at each clinic visit and any diastolic reading of >/= 90 or systolic reading >/= 150 will be considered positive if still elevated after being repeated X3 20 minutes apart and the average of the readings is still positive for HTN. All subjects noted to have HTN will be treated with antihypertensive medications.

Categorical statistical analysis will be performed to determine the relationship between PD and PK markers and outcomes. Univariate summary statistics will be calculated, such as the sample median, standard deviation, minimum, and maximum observations. The dichotomized variables were tabulated as high and low levels or positive and negative expression. Changes over time in continuously distributed biomarker levels will be investigated with the sign's test because of the heavy degree of skewness observed in some of the marginal distributions. Associations between interval quality data with ordinal data will be examined with Spearman's correlation coefficient. Associations between dichotomized biomarkers among themselves and with ordinal subject characteristics such as tumor grade or performance status will be characterized with Kendall's tau-b correlation.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Safety Data Review

A UCI independent data safety committee will review safety data consisting of the reported adverse events, discontinuations and mortality that occur during the course of the protocol. The charter of the committee is to evaluate the safety of the program using

available data from the clinical and SAE databases on a quarterly basis, or more frequently if a safety issue arises. Based on the data review, the committee will make recommendations as to whether any modifications of the trial are warranted.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Written informed consent must be obtained from each subject prior to participation in the study.

10. REFERENCES

Altorki N, Guarino M, Lee P, Pass HI, Filip E, Bauer T, Roychowdhury D,. Zaks T,. Ottesen L, Yankelevitz D. Preoperative treatment with pazopanib (GW786034), A multikinase angiogenesis inhibitor in early-stage non-small cell lung cancer (NSCLC): a proof-of-concept phase II study. J Clin Oncol 26: 2008 (May 20 suppl; abstr 7557).

Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17(7):2105–16.

Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am 2000;6 Suppl 1(1):S11–4.

Atkins MB. Cytokine-based therapy and biochemotherapy for advanced melanoma. Clin Cancer Res 2006;12(7 Pt 2):2353s–8s.

Brick A, Kirkin AF, Zeuthen J, Hou-Jensen K. Expression of basic fibroblast growth factor and vascular endothelial growth factor in primary and metastatic melanoma from the same patients. Melanoma Res 1999;9(4):375–81.

Danson S, Lorigan P. Improving outcomes in advanced malignant melanoma: update on systemic therapy. Drugs 2005;65(6):733–43.

Eggermont AM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years?. Eur J Cancer 2004;40(12):1825–36.

Flaherty KT. Chemotherapy and targeted therapy combinations in advanced melanoma. Clin Cancer Res 2006;12(7 Pt 2):2366s–70s.

Fruehauf JP, Lutzky J, McDermott D.F. et al., Axitinib (AG-013736) in patients with metastatic melanoma: A phase II study. J Clin Oncol 26: 2008 (May 20 suppl; abstr 9006)

Gorski DH, Leal AD, Goydos JS. Differential expression of vascular endothelial growth factor-A isoforms at different stages of melanoma progression. J Am Coll Surgeons 2003;197(3):408–18.

GSK/Novartis Pazopanib Investigator's brochure version 7.0

Harris PA, Boloor A, Cheung M, et al. Discovery fo 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. J Med Chem, 2008, 51(15), 4632-4640.

Hodi FS, Soiffer RJ, Clark J, Finkelstein DM, Haluska FG. Phase II study of

paclitaxel and carboplatin for malignant melanoma. Am JClin Oncol 2002;25(3):283–6.

Homsi J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. Cancer Control 2005;12(4):223–9.

Hutson TE, et al. Pazopanib (GW786034) is active in metastatic renal cell carcinoma (RCC): Interim results of a phase II randomized discontinuation trial (RDT). J Clin Oncol 25; 2007 (June 20 suppl; abst 5031).

Jelic S, Babovic N, Kovcin V, Milicevic N, Milanovic N, Popov I, et al. Comparison of the efficacy of two different dosage dacarbazine-based regimens and two regimens without dacarbazine in metastatic melanoma: a single-centre randomized four-arm study. Melanoma Res 2002;12(1):91–8.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer Statistics 2008. Ca Cancer J Clin 2008; 58:71-96.

Korn EL, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol, 2008. 26(4): 527-34.

Lacal PM, Failla CM, Pagani E, Odorisio T, Schietroma C, Falcinelli S, et al. Human melanoma cells secrete and respond to placenta growth factor and vascular endothelial growth factor. J Invest Dermatol 2000;115(6):1000–7.

Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer 1989;64(10):2024–9.

Mahabeleshwar GH, Byzova TV. Angiogenesis in melanoma. Semin Oncol 2007;34:555-65

Marcoval J, Moreno A, Graells J, Vidal A, Escriba JM, Garcia-Ramirez M, et al. Angiogenesis and malignant melanoma. Angiogenesis is related to the development of vertical (tumorigenic) growth phase. J Cutaneous Pathol 1997;24(4):212–8.

Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma.[see comment][erratum appears in J Clin Oncol 2000 Jun;18(11):2351]. J Clin Oncol 2000;18(1):158–66.

Perez DG, Suman VJ, Fitch TR, Amatruda T 3rd, Morton RF, Jilani SZ, Constantinou CL, Egner JR, Kottschade LA, Markovic SN: Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A. Cancer. 2009 Jan 1;115(1):119-27.

Rao RD, Holtan SG, Ingle JN, Croghan GA, Kottschade LA, Creagan ET, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106(2):375–82.

Salven P, Heikkila P, Joensuu H. Enhanced expression of vascular endothelial growth factor in metastatic melanoma. Br J Cancer 1997;76(7):930–4.

Simonetti O, Lucarini G, Brancorsini D, Nita P, Bernardini ML, Biagini G, et al. Immunohistochemical expression of vascular endothelial growth factor, matrix metalloproteinase 2, and matrix metalloproteinase 9 in cutaneous melanocytic lesions. Cancer 2002;95(9):1963–70.

Slamon D, Gomez HL, Kabbinavar F.F, Amit, O, Richie M, Pandite L, Goodman V. A Randomized Study of Pazopanib + Lapatanib vs. Lapatanib alone in patients with HER2- positive advanced or metastatic breast cancer. J Clin Oncol 26:2008 (May 20, abstr 1016).

Sleijfer S, Papai Z, Le Cesne A et al. Phase II study of pazopanib (GW786034) in
patients with relapsed or refractory soft tissue sarcoma (STS): EORTC 62043. *J. Clin*
Oncol. 2007;25(18S): 10031.

Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol; published online January 25, 2010, DOI:10.1200/JCO.2009.23.9764.

Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update. Eur J Cancer 2013; pii: S0959-8049(12)00980-X. doi: 10.1016/j.ejca.2012.12.010. [Epub ahead of print].

Straume O, Akslen LA. Expresson of vascular endothelial growth factor, its receptors (FLT-1, KDR) and TSP-1 related to microvessel density and patient outcome in vertical growth phase melanomas. Am J Pathol 2001;159(1):223–35.

Suttle B, et al. Phase I study of the safety and pharmacokinetics of paclitaxel or paclitaxel in combination with carboplatin administered in combination with pazopanib (GW786034). J Clin Oncol 25; 2007 (June 20 suppl; abst 14118).

Tan AR, et al. Phase I study of the safety, tolerability, and pharmacokinetics (PK) of weekly paclitaxel administered in combination with pazopanib (GW786034). J Clin Oncol 26; 2008 (May20 suppl; abst 3552).

Varker KA, Biber JE, Kefauver RJ, Lehman A, Young D, Wu HF, Lesinski GB, Kendra K, Chen HX, Walker MJ, Carson WE. A Randomized Phase 2 Trial of Bevacizumab with or without Daily Low-Dose Interferon Alfa-2b in Metastatic Malignant Melanoma. Annals Surg Onc. 2007 Aug 14(8);2367-2376.

Ugurel S, Rappl G, Tilgen W, Reinhold U. Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival. J Clin Oncol 2001;19(2):577–83.

Vlaykova T, Laurila P, Muhonen T, Hahka-Kemppinen M, Jekunen A, Alitalo K, et al. Prognostic value of tumour vascularity in metastatic melanoma and association of blood vessel density with vascular endothelial growth factor expression. Melanoma Res 1999;9(1):59–68.

11. APPENDICES

11.1. Appendix 1: American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) Classification of Melanoma

The existence of an accurate staging system that groups patients of similar risk of disease progression/natural history is a necessary tool for the appropriate selection of optimal treatments. An accurate staging system is also required to appropriately test new therapies in more homogenous patient populations allowing greater clinical relevance to results of clinical trials. Based on data dealing with the natural history of melanoma generated over the past 3-4 years, the AJCC proposed the following revised TNM staging system for melanoma:

Proposed TNM Classification for Clinical Staging of Malignant Melanoma

T classification		
T1	≤ 1.0 mm	A: without ulceration
T1		B: with ulceration or Clarks' level IV or V
T2	1.01-2.0 mm	A: without ulceration
T2		B: with ulceration
T3	2.01-4.0 mm	A: without ulceration
T3		B: with ulceration
T4	>4.0 mm	A: without ulceration
T4		B: with ulceration
N classification		
N1	One lymph node	A: micrometastasis[a] B: macrometastasis[b]
N2	2-3 lymph nodes	A: micrometastasis[a] B: macrometastasis[b] C: in-transit met(s)/satellites(s) *without* metastatic lymph nodes
N3	4 or more metastatic lymph nodes, matted lymph nodes, or combinations of in-transit met(s)/satellite(s), or ulcerated melanoma *and* metastatic lymph node(s)	
M classification		
M1	Distant skin, sub-Q, or lymph node mets	Normal LDH
M2	Lung mets	Normal LDH
M3	All other visceral or any distant mets	Normal LDH Elevated LDH with any M

Mets: metastases

a - Micrometastases are diagnosed after elective or sentinel lymphadencectomy.
b - Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

(Table was reproduced from "A New American Joint Committee on Cancer Staging System for Cutaneous Melanoma", Cancer 88:1484, 2000. Grade B)

Clinical Staging for Cutaneous Melanoma

Clinical Staging[a]			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	M0	M0
IIC	T4b	N0	M0
IIIA	Any T1-4a	N1b	M0
IIIB	Any T1-4a	N2b	M0
IIIC	Any T	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	Any M

Pathologic Staging[b]			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
IIIB	T1-4a	N1b	M0
	T1-4a	N2a	
IIIC	Any T	N2b,N2c	M0
	Any T	N3	
IV	Any T	Any N	Any M

a - **Clinical staging** includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases; by convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
b - **Pathologic staging** includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy, except for pathologic Stage 0 or Stage 1A patients, who do not need pathologic evaluation of their lymph nodes *(Table was reproduced from "A New American Joint Committee on Cancer Staging System for Cutaneous Melanoma", Cancer 88:1484, 2000, grade B).*

11.2. Appendix 2: The Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scales

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.

11.3. Appendix 3: Cockcroft and Gault Formula for Estimated Creatinine Clearance (CrCl)

$$\text{CrCl for males (mL/min)} = \frac{[140 - \text{age (years)}] \times [\text{weight (pounds)}^{a}]}{(72) \times [\text{Serum creatinine (mg/dL)}]}$$

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

For SI units:

$$\text{CrCl for males (mL/min)} = \frac{[140 - \text{age(years)}] \times [\text{weight(kg)}^{1}] \times (1.23)}{[\text{serum creatinine (}\mu\text{mol/L)}]}$$

$$\text{CrCl for females (mL/min)} = \frac{[140 - \text{age(years)}] \times [\text{weight(kg)}^{1}] \times (1.05)}{[\text{serum creatinine (}\mu\text{mol/L)}]}$$

1. If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimate CrCl.

11.4. Appendix 4: New York Heart Association (NYHA) Classification of Congestive Heart Failure

Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

11.5. Appendix 5: Recommendations for Management of Hypertension

The pathogenesis of hypertension induced by angiogenesis inhibitors is likely to be multi-factorial. VEGF and VEGFR-2 are involved in the proper maintenance, differentiation, and function of endothelial cells. Arterial hypertension is characterized by reduced nitric oxide (NO) biosynthesis, activation of the renin-angiotensin-aldosterone system (RAAS), increased vasoconstriction, and microvascular rarefaction of arterioles and capillaries. Microvasular rarefaction in hypertension is partly due to impaired angiogenesis. Hypertension observed with anti-angiogenic agents is thought to be due to decreased bioavailability of endothelium-derived NO, which is a potent vasodilator, as a result of reduced endothelium function by anti-angiogenesis.

Control of Hypertension Prior to Study Entry

For subjects presenting with hypertension, their BP must be adequately controlled to < 150/90 mmHg prior to the first dose of study medication. This can be achieved by adjusting the existing anti-hypertensive medications or adding new one [See below for permitted anti-hypertensive medications and Section 6.3.2 for baseline BP assessment].

Control of Hypertension during Study Treatment

In event hypertension is worsened or emerged during study treatment; the management of hypertension should include two parts: 1. Dose modification of study medication, including interruption, reduction, re-challenge, or discontinuation of study medication [See Section 5.3.1 for guidelines and algorithm]. 2. Management of hypertension with anti-hypertensive medications.

The following antihypertensive medications are **permitted** by the protocol but should be used with **caution:**

- Dihydropyridine calcium channel blockers: felodipine, nifedipine, nicardipine, nimodipine, nitrendipine, amolodipine, nisoldipine, and isradipine.
- Angiotensin II blockers: losartan and irbesartan.
- Beta-blockers: carvedilol, metoprolol, propafenone, propranolol, and timolol.
- Calcium channel blocker: diltiazem and verapamil.

Based on consultation with experts in the field, we recommend the use of dihydropyridine calcium channel blocker and ACE inhibitors as the first line and second line of therapy, respectively, for treatment-related hypertension. The use of non-dihydropyridine calcium channel blockers diltiazem and verapamil are not encouraged. The lead investigator should be contacted if there is any concern or need for clarification.

11.6. Appendix 6: Procedures for Obtaining Urine Protein/Creatinine Ratio

1. Obtain at least 4 mL of a random urine sample (does not have to be a 24-hour urine)
2. Determine protein concentration (mg/dL)
3. Determine creatinine concentration (mg/dL)
4. Divide the value from Step 2 by the value from Step 3 above: urine protein/creatinine ratio = protein concentration (mg/dL)/creatinine concentration (mg/dL)

The urine protein/creatinine ratio directly correlates with the amount of protein excreted in the urine per 24 hours (i.e., a urine protein/creatinine ratio of 1 should be equivalent to 1 g of protein in a 24-hour urine collection).

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an institution, their measurements and reports may need to be requested.

11.7. Appendix 7: Blood Samples for Soluble protein assessments: Procedures for Sampling, Handling, Storage, and Shipment

Plasma samples for analysis of soluble proteins will be obtained at the time points designated in the protocol Table 6. Time and Events Table.

1. An indelible marker should be used to record the patient initials, ID number, collection date, and cycle day on the collection tube prior to collection.
2. Collect 10.0 mL of blood into a sodium heparin tube (green top) at the designated times.
3. After collection, gently invert the tube (15 times) to completely mix blood and anticoagulant.
4. Once the sample has been mixed, it should be placed immediately into an ice bath ensuring that the tube is immersed so that the temperature is kept at 2° C to 8°C during all processing steps.
5. Centrifuge at 3500 rpm at 4°C for 10 minutes.
6. Transfer upper layer using a pipette into 4 Nalgene (2 brown capped, and 2 orange capped) cryovials; split approximately a quarter of the sample into each of the vials.
7. Store tubes at –70°C to –80°C.
8. One brown and one orange capped cryovial (primary sample, larger 3.6 mL tubes) should be shipped on the day of collection and one tube each (back-up sample, smaller 1.8 mL tubes) should be retained at the site in a –70°C or –80°C freezer.

Refer to the study reference binder for sample shipping instructions.

11.8. Appendix 8: Fresh Tissue Samples: Procedures for Sampling, Handling, Storage, and Shipment

After the patient grants informed consent for the biopsy, at least a 0.5-3 cm cube of tumor tissue from a superficial lesion should be obtained by a punch, core, or excisional biopsy. The 4 mm cube should be snap frozen in liquid nitrogen within one hour and stored at -70°C to -80°C. The sample analysis will not be anonymized and will be carried out specifically for the purposes of evaluating correlation of DNA and RNA patterns with clinical response. The samples will not be made available to anyone not associated with this study or external investigators. All materials (DNA and RNA) will be destroyed immediately after analysis. No genetic material will be stored.

11.9. Appendix 9: Biomarker Analysis

ELISA. VEGF and TSP1 production are measured using a human Quantikine ELISA kits (R&D system, Minneapolis MN) per manufacturer's instructions. HIF1α and p53 production are measured using DuoSet IC ELISA kits (R&D system, Minneapolis MN) per manufacturer's instructions.

IHC. All sections are deparaffinized in xylene (Richard Allen, Kalamazoo MI) and rehydrated with increasing concentrations of water in Dehydrant (Richard Allen, Kalamazoo MI) and undergo target retrieval prior to staining. CD31, CD105, and p53 required a standard target retrieval solution (TRS) diluted from 10x (DAKO, Carpinteria CA). TSP1 and VEGF antigen retrieval is performed in a home-brew target retrieval solution, consisting of 1mM EDTA (Sigma, St. Louis MO) in double distilled water titrated to pH 8.0. Melan-A required a high pH target retrieval solution (diluted from 10x, DAKO, Carpinteria CA). The appropriate target retrieval solution is preheated to 95^{o}C in a steamer and slides were incubated in 95^{o}C TRS for 10-20 minutes. Slides are removed from the steamer to cool in the target retrieval solution for an equal amount of time. Slides are rinsed twice in double distilled water and incubated in wash buffer (diluted from 10X, DAKO, Carpinteria CA) for a minimum of 5 minutes prior to staining. All IHC is performed using a DAKO Autostainer (Carpenteria CA).

All other staining is performed using the two-step EnVision+ system (DAKO, Carpinteria CA). In this system, slides are blocked with hydrogen peroxide for 10 minutes to block endogenous peroxidase activity and incubated with primary mouse antibody for an hour. Primary antibody clones and dilutions are as follows: CD31 JC70a 1:50 (DAKO, Carpinteria CA), p53 DO-1 1:2000 (DAKO, Carpinteria CA), TSP1 8A6B 1:200 (Novocastra/Leica, Bannockburn IL), VEGF Ab-7 VG1 1:100 (Neomarkers/Labvision, Fremont CA), HIF1α clone 56 1:50 (BD, San Jose CA), Melan-A A103 1:50 (DAKO, Carpinteria CA). The secondary reagent is an HRP labeled polymer conjugated with goat anti-mouse and anti-rabbit antibodies. This labeled polymer-HRP is incubated for 30 minutes followed by ten minutes of incubation with DAB. Results are compared to appropriate isotype (DAKO, Carpinteria CA) or counterstain only controls. Positive and negative cell line controls are used for each antibody. Slides are counterstained with either methyl green (DAKO, Carpinteria CA) or hematoxylin (DAKO, Carpinteria CA). Slides are dehydrated in increasing concentrations of Dehydrant, cleared in ClearRite (Richard Allen, Kalamazoo MI), and mounted with coverslips (Fisher, Houston TX) using Mounting Media (Richard Allen, Kalamazoo MI).

11.10. Appendix 10: Phamacokinetic Samples: Procedures for Sampling, Handling, Storage, and Shipment.

PK samples will be submitted to the Fruehauf lab for shipping to the reference lab carrying our the pazopanib PK analysis.