SUMMARY OF CHANGES

Date:	August 26, 2020
Document:	NCI Protocol #9048, PhII-122: "A Randomized Phase 2 Study of AMG 386 with or without Continued Anti-Vascular Endothelial Growth Factor (VEGF) Therapy in Patients with Renal Cell Carcinoma Who Have Progressed on Bevacizumab, Pazopanib, Sorafenib, or Sunitinib."
Note:	The following is a Summary of Changes between the 12.23.19 and 8.26.20 versions of protocol

#	Section	Comments
1	Face Page	Changed protocol version to August 26, 2020. Dates in the headers were also changed to 8.26.20.

2	7.1	Insertion of Revised Sorafenib CAEPR (Version 2.10, June 24, 2020):
		• Increase in Risk Attribution:
		  • Changed to Rare but Serious from Also Reported on Sorafenib Trials But With Insufficient Evidence for Attribution: Injury, poisoning and procedural complications - Other, specify (wound healing complication)
		• Provided Further Clarification:
		  • Wound complication reported under (Also Reported on Sorafenib Trials But With Insufficient Evidence for Attribution) is now reported as Injury, poisoning and procedural complications - Other, specify (wound healing complication) under (Rare but Serious).

NCI Protocol #: 9048

Local Protocol #: PhII-122

TITLE: A Randomized Phase 2 Study of AMG 386 with or without Continued Anti-Vascular Endothelial Growth Factor (VEGF) Therapy in Patients with Renal Cell Carcinoma Who Have Progressed on Bevacizumab, Pazopanib, Sorafenib, or Sunitinib

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NCI Supplied Agent:

AMG 386 (NSC 751173)

Commercial Agents:

Patients will use commercial supply of the following agents:
Bevacizumab, Genetech/Roche
Pazopanib, GlaxoSmithKline

Sorafenib, Bayer Healthcare/Onyx Pharmaceuticals
Sunitinib, Pfizer Pharmaceuticals

Protocol Type / Version # / Version Date:		
	Initial Protocol	January 19, 2012
	Response to Consensus Review	March 9, 2012
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	Amendment 1	April 17, 2012
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	Amendment 10 (RA)	August 26, 2014
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	Amendment 14 (RRA)	February 10, 2016
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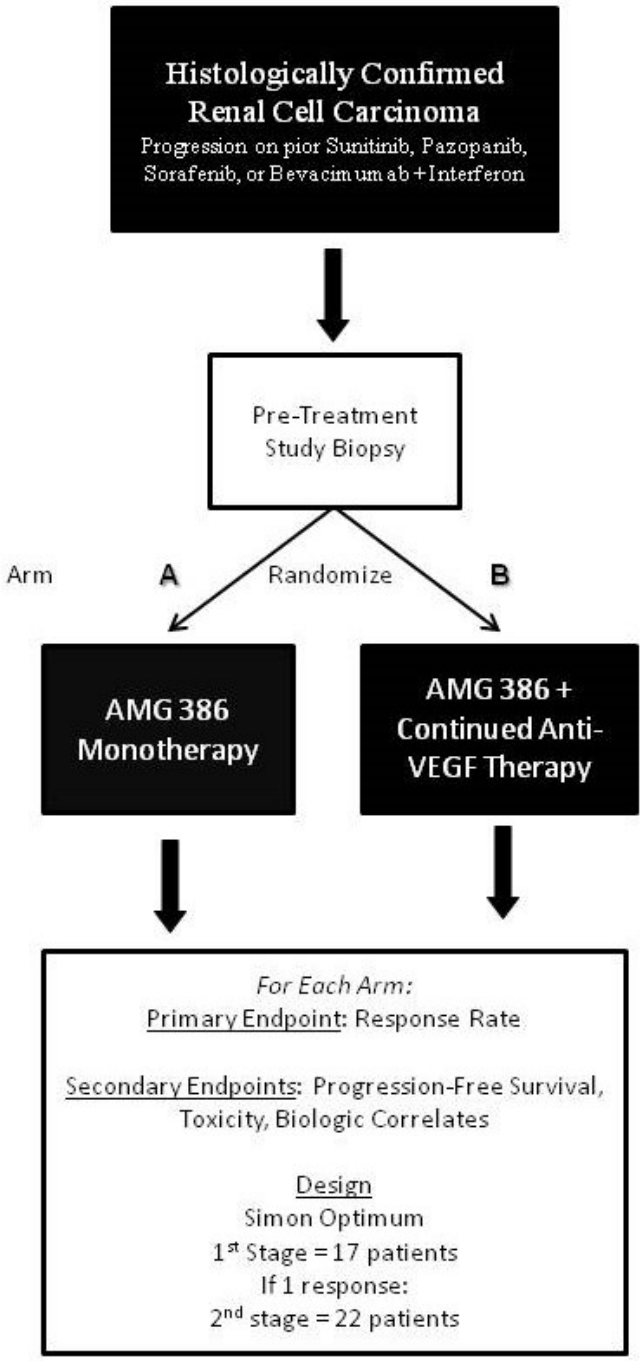
	Amendment 18 (RRA)	August 4, 2017
	Amendment 19	March 13, 2018
	Amendment 20 (RRA)	September 11, 2018
	Amendment 21 (RA)	March 19, 2019
	Amendment 22 (RA)	March 29, 2019
	Amendment 23 (RA)	July 11, 2019
	Amendment 23 (RRA)	December 23, 2019
	Amendment 24 (RRA)	August 26, 2020

SCHEMA


Histologically Confirmed
Renal Cell Carcinoma
Progression on pior Sunitinib, Pazopanib, Sorafenib, or Bevacimumab+Interferon
Pre-Treatment
Study Biopsy
Arm
A
Randomize
B
AMG 386
Monotherapy
AMG 386 +
Continued Anti-
VEGF Therapy
For Each Arm:
Primary Endpoint: Response Rate
Secondary Endpoints: Progression-Free Survival, Toxicity, Biologic Correlates
Design
Simon Optimum
1st Stage = 17 patients
If 1 response:
2nd stage = 22 patients

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1. OBJECTIVES

1.1. Primary Objective

To evaluate the overall response rate (CR + PR) of AMG 386 alone and in combination with continuation of previously administered bevacizumab, pazopanib, sorafenib, or sunitinib in advanced renal cell carcinoma.

1.2. Secondary Objectives

1.2.1 To evaluate progression free survival in each arm.
1.2.2 To evaluate the tolerance and toxicity of AMG 386 alone and in combination with continuation of the prior VEGF targeted agent.

1.3. Correlative Objectives

1.3.1 To evaluate the association between pretreatment tumor gene expression levels and response to AMG 386 in combination with continuation of the prior VEGF targeted agent.
1.3.2 To evaluate the association between SNPs in angiogenic genes and response to AMG 386 in combination with continuation of the prior VEGF targeted agent.
1.3.3 To compare changes in circulating angiogenic factors in patients treated with AMG 386 monotherapy to those treated with AMG 386 in combination with VEGF-targeted therapy.
1.3.4 To compare expression of angiogenic genes from archival tumor specimens to the expression in biopsy specimens obtained after progression on anti-VEGF therapy.

2. BACKGROUND

2.1. Advanced Renal Cell Carcinoma

Over 60,000 new cases of renal cell carcinoma (RCC) will be diagnosed in the United States in 2011 and the disease will account for approximately 13,000 deaths (Siegel et al. 2011). Surgery is a potentially curative therapeutic option for localized disease, although recurrence after nephrectomy occurs in up to 50% of cases. No adjuvant therapy has been shown to reduce this risk. Additionally, as many as one-third of newly diagnosed patients with RCC have metastases present at the time of diagnosis. For these patients, the disease is unlikely to be cured. In the cytokine era, investigators at the Memorial Sloan Kettering Cancer Center (MSKCC) developed a prognostic scoring system that is comprised of 2 clinical variables: performance status and time from diagnosis to treatment; as well as 3 laboratory variables: the levels of lactate dehydrogenase, hemoglobin, and calcium. Using this system, patients can be categorized into three groups according to risk. Similar risk factors were obtained when these analysis were repeated for those receiving anti-vascular

endothelial growth factor (VEGF) therapy.

Treatment of advanced RCC may involve multiple modalities. Debulking nephrectomy and surgical resection of limited metastatic disease improve outcomes in selected cases. Immune therapy with IL-2 provides a small, but consistent, chance of complete response (CR) and prolonged disease free survival. The development of a number of new agents for the treatment of advanced RCC in the past several years has resulted from an improved understanding of the molecular underpinnings of the disease. Clear cell RCC is frequently associated with mutations in the von Hippel Lindau (VHL) gene that results in deregulated signaling through hypoxia inducible factor (HIF). This potent signaling molecule increases transcription of multiple proangiogenic factors including VEGF, platelet-derived growth factor (PDGF), and transforming growth factor alpha (TGFα). With the observation that angiogenic signaling was key to the development and progression of advanced RCC, a number of anti-angiogenic agents have been developed and tested.

Multiple small molecule kinase inhibitors have recently obtained regulatory approval for the treatment of RCC including pazopanib (Votrient™, GlaxoSmithKline), sorafenib (Nexavar®, Bayer/Onyx Pharmaceuticals), and sunitinib (Sutent®, Pfizer Corporation). Although the spectrum of target affinity differs amongst the agents, a common feature is inhibition of signaling through the VEGF pathway. Additionally, the VEGF-A ligand sequestering antibody bevacizumab (Avastin®, Genentech/Roche), demonstrated benefit in the management of advanced RCC in combination with interferon. One of these anti-VEGF agents is now the standard of care for the initial treatment of most patients with newly diagnosed advanced RCC.

Using analogous reasoning, two inhibitors of the mammalian target of rapamycin (mTOR) have also recently been developed for the management of patients with advanced RCC: temsirolimus (Torisel®, Pfizer Corporation), and everolimus (Affinitor®, Novartis Pharmaceuticals). The mTOR pathway is abnormally regulated in RCC, and signaling through the phosphatidlyinositol-3-kinase(PI3K)-Akt-mTOR pathway is a important driver of proliferation and angiogenesis in the setting of hypoxia. Temsirolimus is considered a standard initial treatment for patients with MSKCC poor prognosis advanced RCC and everolimus is currently an approved agent for patients previously treated with sunitinib or sorafenib.

Despite these advances in therapy, the majority of cases of advanced RCC remain incurable and therapeutic resistance invariable develops. Resistance to anti-VEGF therapy may develop from selection for or up-regulation of alternative pro-angiogenic pathways, recruitment of bone marrow derived vascular progenitors and pro-angiogenic monocytes, increased involvement of pericytes in blood vessel stability, and increased capacity for invasion without metastasis. The recruitment of alternative angiogenic pathways is as a potential mechanism for failure of anti-VEGF therapy. A number of inhibitors of these pathways have been developed and are in clinical testing. Furthermore, it is not presently known whether continued VEGF pathway inhibition is required for the clinical efficacy of antiangiogenic agents that

inhibit these alternative pathways.

2.2. AMG 386

AMG 386 (previously named 2XCon4[C]) is a novel peptide-Fc fusion protein, or peptibody. The molecule is a non-glycosylated homodimer engineered by fusing an IgG1 Fc domain to 4 copies of an anti-angiopoietin (Ang)-2 (Ang2) peptide. AMG 386 sequesters Ang1 and Ang2, thereby preventing their interaction with Tie2 and inhibiting tumor endothelial cell (EC) proliferation and tumor growth. The neutralization potency of AMG 386 is greater against Ang2 (50% inhibitory concentration [IC_{50}]=0.023 nM) than Ang1 (IC_{50}=0.9 nM). The potency against Ang2 is similar across species between humans, mice, rats, and cynomolgous monkeys, while the potency against Ang1 is similar between mice and humans (Investigator's Brochure 2011).

Angiopoietins as targets of anticancer therapy

The Ang family has four members (Ang 1-4), with Ang1 and 2 being the best understood (Augustin et al. 2009; Eklund et al. 2006; Huang et al. 2010; Yancopoulos et al. 2000). Ang1 and Ang 2 are ligands of Tie2, a tyrosine kinase (TK) receptor expressed on ECs. Ang1 is mainly derived from perivascular cells (pericytes or smooth muscle cells); it acts as an agonist of Tie2 and promotes vascular maturation and stabilization. Ang2 is primarily produced in activated ECs, and is thought to be an antagonist of Tie2. By displacing Ang1 from Tie2, Ang2 induces vascular plasticity and renders ECs more responsive to angiogenic signals such as VEGF. In certain contexts, Ang2 may also act as an agonist of Tie2. The precise signal transduction pathway downstream of Ang-Tie2 interaction is unknown; the PI3K-AKT-mTOR pathway has been implicated in most studies. While the two angiopoietins may seem to have contradictory effects on Tie2, they act complementarily in the angiogenesis process, from vascular formation to vascular maturation: Ang2 promotes EC proliferation, sprouting, and neoangiogenesis, while Ang1 maintains EC survival, pericyte coverage, and vascular integrity. Angiopoietins are also required for the formation of lymphatic vessels. Ang2 ablation in mice was compatible with live birth, but most mice died within 2 weeks with severe chylous ascites and peripheral lymphedema (Gale et al. 2002). Overexpression of Ang was found to be associated with lymph node metastases in early gastric (Jo et al. 2009) or breast cancers (Sfiligoi et al. 2003). In addition, Ang1 and Ang2 have been shown to interact with integrin (α5vβ3 or α5β1) on ECs or nonvascular cells; these interactions were implicated in the survival of certain neuronal cells (Dallabrida et al. 2005; Lee et al. 2006), cardiomyocytes, and tumor cells (Imanishi et al. 2007), but the precise mechanisms have not be elucidated.

Preclinical studies with Ang1- and Ang2-specific antagonists have suggested that Ang2 is involved in EC proliferation and angiogenesis in cancers, and that inhibition of Ang2 may have therapeutic benefit (Oliner et al. 2004). Angiopoietins may also promote tumor growth through non-vascular mechanisms. Recent studies reported

that Tie2-expressing monocytes (TEMs) can be recruited to tumor sites through the chemo-attractant action of angiopoietins (De Palma et al. 2008). In tumor xenograft models, TEMs purified from human tumor specimens markedly promoted angiogenesis, suggesting a potentially critical role of TEMs in human cancer progression (De Palma et al. 2008; Lewis et al. 2007; Venneri et al. 2007).

Studies with anti-VEGF agents in tumor models suggest that Ang1 and Ang2 may play a role in tumor survival under VEGF inhibition. In an orthotopic tumor model (Huang et al. 2009), while an Ang1 agonist did not alter tumor growth by itself, it was found to attenuate the antitumor effect of VEGF Trap and protect the tumor vessels from regression. In the U87 glioma model, ectopic expression of Ang2 increased vascular density without impact on tumor growth; however, the presence of Ang2 compromised the activity of a VEGFR2 inhibitor, suggesting that blocking Ang2 along with VEGF may lead to enhanced therapeutic effect (Chae et al. 2010). In patients with renal cell cancer (RCC), circulating Ang2 levels were initially decreased after treatment with sunitinib but subsequently increased at the time of tumor progression (Bullock et al. 2010).

Overexpression of Ang1, Ang2, or Tie2 can be found in tumor tissues, but the levels and sites of expression (ECs, stromal cells, or tumor cells) are highly variable among individual patients and tumor types. Increased levels of Ang2 in the tumor or in circulation have been associated with higher grade, later stage, and poorer survival in several malignancies, including melanoma (Helfrich et al. 2009), glioma, gastric cancer (Etoh et al. 2001; Jo et al. 2009), breast cancer, bladder cancer (Oka et al. 2005; Szarvas et al. 2008), and acute myeloid leukemia (AML) (Hou et al. 2008; Loges et al. 2005). In general, Ang2 or Tie2 expression is confined to ECs or stromal cells, but ectopic expression in tumor cells has also been reported (e.g., gastric cancer, inflammatory breast cancer, and thyroid cancer). The functional relevance of Tie2 expression on tumor cells is unclear. A summary of Ang1, Ang2, and Tie2 expression data in various human cancers has been published (Augustin et al. 2009).

Nonclinical Studies of AMG 386

In vitro efficacy: AMG 386 does not alter the *in vitro* growth of human cancer cell lines, including A431 (uterine epidermoid carcinoma) and Colo205 (colon carcinoma), indicating that the mechanism of action of AMG 386 is not likely to be through a direct antitumor effect (Investigator's Brochure 2011).

In vivo efficacy: As a single agent, AMG 386 significantly inhibited VEGF-induced rat corneal angiogenesis and inhibited the growth of multiple tumor xenografts in nude mice, including Colo205, A341, OVCAR-3 SQ3 (ovarian carcinoma), and HT29 (colon carcinoma). The antitumor effect in the Colo205 model was associated with a reduction of EC proliferation and significant increases in tumor cell apoptosis and necrotic tumor fraction; no increase in EC apoptosis suggests that AMG 386 prevents tumor growth via inhibition of angiogenesis. Maximum efficacy in Colo205 tumor-bearing mice occurred at 0.6 mg/kg administered subcutaneously (SC) twice

weekly, which resulted in a minimum observed serum concentration (C_{min}) of 3 mcg/mL. No delay in tumor growth was observed with AMG 386 treatment in several tumor models, including U-87 MG (glioblastoma), Calu6 (lung carcinoma), Daudi (B-cell lymphoma), and MesSa/Dx5 (uterine sarcoma) (Investigator's Brochure 2011).

The combination of AMG 386 with VEGF/VEGFR inhibitors was associated with greater antitumor activities when compared with each agent alone. In the HT29 model, AMG 386 in combination with motesanib (a multi-kinase inhibitor against VEGFR/PDGFR/cKit) showed superior antitumor activity in the HT29 model. Similarly, the combination of AMG 386 with bevacizumab in Colo205 xenografts also resulted in significantly improved efficacy. In another experiment in the Colo205 model, combination of bevacizumab and an Ang2-specific peptide (L1-7[N]) demonstrated that the enhanced antitumor effect was associated with significantly lower vascular sprouting and more profound vascular regression (Hashizume et al. 2010).

Combinations of AMG 386 with irinotecan, fluorouracil (5-FU), and docetaxel have also been tested in the Colo205 model. Preliminary data suggest neither antagonism of single-agent efficacy nor gross evidence of increased toxicity upon combining the agents, but the study design did not allow for conclusions regarding additive activity to be made (Investigator's Brochure 2011).

Preclinical pharmacology: Pharmacokinetics (PK) studies were conducted in Sprague-Dawley rats and cynomolgus monkeys (Investigator's Brochure 2011). Single-dose intravenous (IV) administration of AMG 386 exhibited dose-linear PK over dose ranges of 1 to 100 mg/kg (rats) and 5 to 100 mg/kg (monkeys). The mean terminal elimination half-life ($t_{1/2}$) was 97.5 and 49.5 hours in rats and monkeys, respectively. The mean volume of distribution value after the first dose (V_0) was similar to the plasma volume but increased by 4-5 fold steady state (V_{ss}), suggesting that AMG 386 distributes extravascularly.

No accumulation of AMG 386 was observed after twice-weekly IV administration to rats (3 to 300 mg/kg) and monkeys (25 to 300 mg/kg) for 4 weeks. After 13 weeks, however, moderate accumulation (accumulation ratio [AR] range, 2.03 to 2.77) was observed in rats; low accumulation (AR range, 1.19 to 2.09) was observed in monkeys.

Unlike full IgG antibodies, the kidneys may contribute to the overall clearance of AMG 386. PK profiles in splenectomized rats indicate that the spleen is not involved in the elimination of AMG 386. In nephrectomized rats, total clearance was decreased by approximately 30%. These values were 14-18 fold higher in the neonatal constant region fragment (Fc) receptor (Fc-Rn) knockout mice, indicating the Fc-Rn receptor contributes to the sustainability of circulating AMG 386 levels after IV administration of 3 and 10 mg/kg to mice (Investigator's Brochure 2011).

Preclinical toxicology: In preclinical toxicology studies in adult monkeys and dogs, AMG 386 was well tolerated, with findings consistent with the mechanisms of action (see Investigator's Brochure, 2011, Section 5.3 for details).

As with other antiangiogenic agents, administration of AMG 386 in developing monkeys has shown dose-dependent, premature closure of the physeal growth plate. AMG 386 is also detrimental to fetal growth and has potential impact on the reproductive system (see Investigator's Brochure, 2011, Section 5.3 for details).

Clinical Studies of AMG 386

There are a total of 16 studies sponsored by Amgen with AMG 386 as monotherapy or in combination regimens. Two studies have been completed, while 14 are ongoing. The trials (six phase 1, seven phase 2, two phase 3, and one unspecified) have included: 1) phase 1 trials for single agent, combination with anti-VEGF agents (AMG 706 [motesanib], sorafenib, sunitinib, and bevacizumab), or combination with chemotherapy (carboplatin/paclitaxel, docetaxel, paclitaxel/trastuzumab, capecitabine/lapatinib, topotecan, and pegylated liposomal doxorubicin [PLD]); 2) phase 2 trials for combination with chemotherapy in ovarian, gastric, colorectal, and breast cancer; 3) phase 2 trials in combination with VEGFR tyrosine kinase inhibitors (TKIs) in RCC and hepatocellular carcinoma (HCC); and 4) phase 3 trials in combination with chemotherapy in ovarian cancer (Investigator's Brochure 2011).

PK, immunogenicity, and maximum tolerated dose (MTD) in humans: In the phase 1 **Study 20040169**, 32 patients with advanced solid tumors received AMG 386 monotherapy in escalating dose cohorts from 0.3 to 30 mg/kg IV weekly. AMG 386 exposure was dose proportional, and the total serum clearance appeared to be similar across doses, suggesting that AMG 386 exhibited linear PK. The mean $t_{1/2}$ was 3.1 to 6.3 days, and the serum steady state level (C_{ss}) was reached after four weekly doses. The average minimum observed concentration (C_{min}) increased approximately proportionately with increasing dose. At the initially selected phase 2 doses of 3 and 10 mg/kg IV weekly, the mean C_{ss} was 10.2 mcg/mL and 26.6 mcg/mL, respectively. Across studies, exposure to weekly IV doses of AMG 386 at 3 and 10 mg/kg (and 15 mg/kg, based on more limited experience) has been consistent with the approximately dose-proportional PK and minimal accumulation observed in **Study 20040169**. Population PK modeling in several studies has identified baseline creatinine clearance (CrCl) as a significant covariate for AMG 386 Cl.

No PK alterations of AMG 386 at 10 mg/kg have been demonstrated in coadministration with other agents, including VEGF inhibitors (motesanib, sorafenib, sunitinib, and bevacizumab) and/or chemotherapeutic agents (FOLFOX-4 [oxaliplatin, leucovorin, and infusional 5-fluorouracil (5-FU)], FOLFIRI [5-FU, leucovorin, and irinotecan], paclitaxel, docetaxel, carboplatin, cisplatin, PLD, topotecan, and capecitabine). Linear interpolation to compare 15 mg/kg of AMG 386 with monotherapy data additionally suggests no evidence of drug interaction. There has been no conclusive evidence of a marked PK interaction between AMG 386 and

other targeted or chemotherapeutic agents after coadministration.

As of March 30, 2011, no patients have developed neutralizing antibodies in any open-label or blinded AMG 386 studies. Of the 703 patients across nine studies who had serum samples tested for immunogenicity, 32 patients developed binding antibodies to AMG386.

At doses up to 30 mg/kg weekly in the first-in-human phase 1 **Study 20040169** and Japanese phase 1 **Study 20060212**, the MTD was not reached.

Pharmacodynamics in humans: There have been limited pharmacodynamic studies with AMG 386. In the completed phase 1 single agent trial (Study 20040169) (Herbst et al. 2009), the post-treatment effects of AMG 386 were assessed by DCE-MRI and ^{18}F-FDG PET, and angiogenic cytokine and apoptosis marker levels in blood. Of the 12 patients with interpretable serial DCE-MRIs, 10 patients were treated at 30 mg/kg and the others at 1 mg/kg and 3 mg/kg. Vascular response, as measured by volume transfer constant (K^{trans}) and initial area under the curve (IAUC) changes, were demonstrated in all patients, but a dose-effect correlation (or lack thereof) cannot be made due to small numbers. A significant vascular effect (i.e., $\geq$20% reduction in median K^{trans}) was seen in 7/12 patients on Day 2, 3/6 patients at Week 4, and 5/8 patients at Week 8.

Serial blood levels of several angiogenic cytokines (*e.g.*, VEGF and placental growth factor [PlGF], serum VCAM-1 [sVCAM-1], Ang1, and Ang 2) are being assessed in ongoing phase 1b and 2 studies. Small but significant changes in PlGF and sVCAM-1 have been observed in response to treatment with AMG 386. The correlation of these and other potential markers with clinical response will require larger studies and more optimal sampling time.

Clinical activity of AMG 386:

Phase 1 study of single agent AMG 386 in solid tumors (Study 20040169). In the primary analysis (September 6, 2006), 29 patients were evaluable for tumor response. One patient with advanced, refractory ovarian cancer treated at 30 mg/kg achieved a partial response (PR) after 68 weeks that lasted up to 156 weeks when she withdrew from study; CA125 response occurred earlier, at week 4. Four patients had stable disease (SD) for >16 weeks: one each with soft tissue sarcoma, thyroid cancer, pseudomyxoma, and submandibular adenocarcinoma.

Phase 1 study of single agent AMG 386 in Japanese patients with advanced solid tumors (Study 20060212). Preliminary data have recently been presented (Toshihiko *et al.*, 2011). Among the 18 patients enrolled in three dose cohorts (3, 10, or 30 mg/kg), two patients achieved PR (one patient with colon cancer treated at 3 mg/kg, and one patient with bladder cancer treated at 30 mg/kg); these two patients were continuing the study treatment for 56 weeks and 24 weeks, respectively. Two patients had a best response of SD, and 14 patients experienced PD.

Phase 1b dose-escalation study of AMG 386 (3-10 mg/kg weekly) in combination with standard phase 2 doses of bevacizumab (15 mg/kg every 3 weeks), **sunitinib** (50 mg daily for 4 out of 6 weeks), or **sorafenib** (400 mg twice daily [BID]) (Study 20050170). A preliminary analysis of efficacy among 30 patients with metastatic RCC was conducted using data available as of March 19, 2010. Of the 15 patients who received sorafenib in combination with AMG 386, 5 patients had PRs, 9 patients had SD, and 1 patient experienced PD. Of the 15 patients who received sunitinib in combination with AMG 386, 1 patient had a CR, 7 patients had PRs, 6 patients had SD, and 1 patient experienced PD. Two patients with advanced squamous cell carcinoma of the head and neck treated with AMG386 and bevacizumab combination developed fatal arterial hemorrhage and tumor hemorrhage; the events were thought to be due to bevacizumab or the combination.

Phase 2 randomized, double-blind, placebo-controlled study in recurrent ovarian cancer patients combining paclitaxel (80 mg/m2 weekly) and AMG 386 (3 or 10 mg/kg weekly) or placebo (Study 20060342). The primary analysis (for data as of October 21, 2009) showed a strong trend toward progression-free survival (PFS) improvement for the paclitaxel + AMG 386 arms (combined) *vs.* paclitaxel + placebo (hazard ratio [HR], 80% CI: 0.761 [0.59, 0.98]; *P*=0.165); median PFS was 5.7, 7.2, and 4.6 months in the AMG 386 3 mg/kg, 10 mg/kg, and placebo groups, respectively. Of the 16 subjects from the paclitaxel + placebo arm who crossed over, median PFS was 2.6 months. The ORR was 19%, 37%, and 27% in the AMG 386 3 mg/kg, 10 mg/kg, and placebo groups, respectively (Karlan et al. 2011). PK analysis revealed a significant correlation between AMG 386 exposure and efficacy (Lu *et al.,* 2010). While patients with low steady state AUC (AUC_{ss}) (<9.6 mg•h/mL) of AMG 386 had a modest difference in PFS compared to the control (5.7 *vs.* 4.6 months, HR 0.81, *P*=0.31), those with high AUC_{ss} (≥9.6 mg•h/mL) exhibited greater PFS improvement above chemotherapy alone (8.1 *vs.* 4.6 months, HR 0.76, *P*=0.14). The apparent dose-efficacy and exposure-efficacy relationships observed here prompted the exploration of higher doses of AMG 386 in subsequent trials. Subsequently, a dose of 15 mg/kg has been selected to begin the phase 3 trials of AMG 386 and chemotherapy in first line ovarian cancer.

Phase 2 randomized, double-blind, multi-center phase 2 study combining sorafenib 400 mg orally (PO) BID and weekly AMG 386 (3 or 10 mg/kg) or placebo in RCC (Study 20060159). The primary analysis (for data as of February 22, 2010) showed no difference in median PFS between individual treatment groups (median PFS: 8.5, 9, and 9 months for the AMG 386 3 mg/kg, 10 mg/kg, and placebo groups, respectively). However, the ORR was higher for AMG 386 at 3 mg/kg (37%) and 10 mg/kg (38%) *vs.* placebo (24%). A phase 2 study of AMG 386 (doses up to 15 mg/kg) with sunitinib is also ongoing (Study 20080579).

Phase 2 randomized, double-blind, placebo-controlled study in gastric cancer (Study 20060439). The primary analysis (for data as of December 15, 2009) showed

no improvement in PFS for patients on cisplatin 80 mg/m^2 and capecitabine 1000 mg/m^2 BID with AMG 386 (3 or 10 mg/kg) or placebo. Earlier discontinuation of study drugs in the AMG 386 arms due to poor tolerability of the combination is likely to have contributed to the observed lack of efficacy and decreased median overall survival (OS) observed for the chemotherapy + AMG 386 3 mg/kg and chemotherapy + AMG 386 10 mg/kg arms (9.4 and 9.1 months, respectively) *vs.* the chemotherapy + placebo arm (12.8 months). Common adverse events leading to discontinuation of investigational product included pulmonary embolism (2%, 5%, 4% of patients in the groups receiving AMG 386 3 mg/kg, AMG 386 10 mg/kg, and placebo, respectively), diarrhea (5%, 2%, 0%), and nausea (3%, 4%, 0%). No single specific toxicity appeared to account for the reduced tolerability of regimens containing AMG 386, and no synergistic toxicities were observed between AMG 386 and chemotherapy.

AMG 386 Safety Profile

At the time of study-respective data cutoff dates for safety and efficacy data (Investigator's Brochure 2011), a total of 1190 patients had been exposed to either AMG 386 or placebo in open-label (343 patients) and unblinded (847 patients) phase 1 and phase 2 studies. Analysis pools for potential and identified risks associated with AMG 386 administration were comprised of 32 patients from monotherapy studies; 293 patients from open label, combination therapy studies; and 847 patients (582 administered AMG 386, and 265 administered placebo) from unblinded, placebo-controlled, combination therapy studies (Investigator's Brochure 2011).

Overall, AMG 386 up to 10 mg/kg weekly is well tolerated as monotherapy or in combination with VEGF inhibitors or chemotherapy. Single agent use at 30 mg/kg also appeared tolerable in the phase 1 trials with a total of 22 patients treated at this dose level (**Study 20040169** and **Study 20060212**).

AMG 386 does not appear to cause hypertension as typically observed with anti-VEGF agents. A unique adverse effect of AMG 386 is edema, which is believed to be due to the target effect on the lymphatic system. Adverse events of proteinuria were not observed in the monotherapy setting, and were reported in 3% and 2% of patients who received AMG 386 in combination with other agents in open-label and blinded studies, respectively. Proteinuria was mild to moderate, non-serious, and did not result in discontinuation of AMG 386.

Safety data for higher doses of AMG 386 (15 and 30 mg/kg) in combination regimens are pending.

A Comprehensive Adverse Events and Potential Risks (CAEPR) list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Details of identified risks (edema, ascites, and pleural effusion) and potential risks are described below.

Edema (identified risk): Ang1 and Ang2 contribute to the normal development of the lymphatic system; Ang2 knockout mice display defects in the lymphatic system, including chylous ascites, hypoplasia of the lymphatic vasculature, and peripheral lympedema (Gale et al. 2002). Edema events occurred in 34% of patients receiving AMG 386 monotherapy and in 46% of patients who received AMG 386 in combination with other agents in open-label studies. In each of the five unblinded studies, a higher incidence of edema was observed in the AMG 386 arms (combined) *vs.* the placebo arms (Table 2-1).

The most common manifestation is peripheral edema, although facial edema, periorbital edema, and penile edema were also reported. The majority of cases were mild to moderate in severity and did not result in permanent discontinuation of investigational product. Current toxicity management guidelines are for investigators to continue AMG 386 for Grades 1 and 2 edema, and to discontinue AMG 386 only for Grade 3 edema.

Ascites (identified risk): Approximately 10% of all cases of ascites are due to cancer, with the most common primary tumor types being ovarian (37%), pancreaticobiliary (21%), gastric (18%), esophageal (4%), colorectal (4%), and breast (3%). Ascites adverse events have been observed for 3% of patients receiving AMG 386 monotherapy, and 8% of patients receiving AMG 386 in combination with other agents in open-label studies. The incidence of ascites in the five unblinded studies is shown in Table 2-1.

Pleural effusion (identified risk): Historically, pleural effusion has been observed in cancer patients with advanced disease. Pleural effusion has been reported for 6% of patients receiving AMG 386 monotherapy, and 6% of patients receiving AMG 386 in combination with other agents in open-label studies; 1% of patients in open-label studies had events of "malignant pleural effusion." The incidence of pleural effusion in unblinded studies is shown in Table 2-1. One fatal event of pleural effusion occurred in a patient with RCC and bilateral lymphangitic carcinomatosis (Study 20080579); the investigator did not consider the event to be related to AMG 386 treatment.

A number of potential risks have been analyzed in AMG 386 trials. The findings are as follows:

Infusion reaction or allergic response: Adverse events consistent with possible infusion reaction were observed for 6% of patients receiving AMG 386 monotherapy, and 2% of subjects who received AMG 386 in combination with other agents in open-label studies; these events included hypersensitivity, infusion-related reaction, and dyspnea and were of severity grade 1 or 2. In the five unblinded studies, the incidence of adverse events consistent with possible infusion reaction was similar or less in the AMG 386 (combined) arms *vs.* the placebo arms; the events included bronchospasm, chills, infusion related reaction, pyrexia, dyspnea, hypersensitivity,

and drug hypersensitivity. No fatal infusion reactions have been reported. One patient developed grade 3 hypotension as part of a possible infusion reaction (Study 20080579). That patient received concomitant methylprednisolone for laryngeal spasms and hot flushes.

Proteinuria: Treatment-emergent adverse events of proteinuria have been observed in clinical studies of AMG 386. Proteinuria has not been reported in patients receiving AMG 386 monotherapy, but it was observed in 4% of patients who received AMG 386 in combination with other agents in open-label studies. The incidence of proteinuria in the five unblinded studies is shown in Table 2-1. The majority of proteinuria events were mild to moderate, nonserious, and did not result in discontinuation of the investigational product.

Gastrointestinal perforation: No patients receiving AMG 386 monotherapy, and 2% of patients who received AMG 386 in combination with other agents in open-label studies, experienced gastrointestinal perforation events. In the five unblinded studies, the incidence of gastrointestinal perforation was similar between the AMG 386 arms (combined) *vs.* the placebo arms (Table 2-1).

One event of gastrointestinal perforation occurred in a patient enrolled in a study of AMG 102 (anti-hepatocyte growth factor/scatter factor neutralizing antibody) who was misdosed by a clinical site and received AMG 386 in addition to AMG 102. Another patient with advanced ovarian cancer who was receiving AMG 386 10 mg/kg in combination with PLD had a fatal event of intestinal perforation.

Hemorrhage: No subjects receiving AMG 386 monotherapy, and 14% of patients who received AMG 386 in combination with other agents in open-label studies, had hemorrhage events. In the five unblinded studies, the incidence of hemorrhage was similar or lower in the AMG 386 arms (combined) *vs.* the placebo arms (Table 2-1). The majority of events were mild to moderate in severity. However, fatal hemorrhage has been observed on the AMG 386-containing arms (see below).

The hemorrhage event with the highest incidence overall was epistaxis; incidence varied among studies, from 0% in Study 20040169 (AMG 386 monotherapy) to 49% in the blinded arms of Study 20060341 (AMG 386 or placebo in combination with paclitaxel and bevacizumab).

Five fatal events of hemorrhage have occurred. Two of the events (hematemesis and gastric hemorrhage, in gastric cancer patients receiving chemotherapy + AMG 386 in Study 20060439) were not considered by the investigator to be related to AMG 386. The other three events were considered possibly related to the study product: two patients with advanced squamous cell carcinoma of the head and neck treated with AMG 386 and bevacizumab combination developed fatal arterial hemorrhage and tumor hemorrhage (Study 20050170); and the other patient with metastatic breast cancer in the lungs treated with AMG 386, paclitaxel, and bevacizumab combination developed fatal hemoptysis (Study 20060341). Since hemorrhage is a recognized

adverse event of agents targeting VEGF (Avastin(R) Prescribing Information 2011), interpreting the relationship of these events to AMG 386 is confounded.

Pulmonary embolism: No subjects receiving AMG 386 monotherapy, and 1% of patients who received AMG 386 in combination with other agents in open-label studies, had events of pulmonary embolism. In most of the five unblinded studies, the incidence of pulmonary embolism in the AMG 386 arms (combined) *vs.* the placebo arms (Table 2-1).

Table 2-1: Incidence of selected AEs (all grades) of interest in five randomized phase 2 trials that have been unblinded

	Study 20060342 (ovarian ca)		**Study 20060159** (RCC)		**Study 20060439** (gastric ca)		**Study 20060341** (Her2- breast ca)		**Study 20070307** (colorectal ca)	
	Paclitaxel + AMG 386 (3 or 10 mg/kg)	Paclitaxel	Sorafenib + AMG 386 (3 or 10 mg/kg)	Sorafenib	Cisplatin/ gemcitabine + AMG 386 (3 or 10 mg/kg)	Cisplatin / gemcitabine	Paclitaxel + Bevacizumab + AMG 386 (3 or 10 mg/kg)	Paclitaxel + Bevacizumab	FOLFIRI + AMG 386 (10 mg/kg)	FOLFIRI
Edema	71%	35%	32%	20%	32%	15%	62%	29%	26%	6%
Ascites	10%	4%	1%	0%	5%	2%	2%	3%	2%	4%
Pleural effusion	6%	0%	6%	0%	4%	0%	7%	0%	0%	0%
Proteinuria	7%	4%	15%	8%	1%	2%	4%	2%	1%	0%
GI perforation	0%	2%	2%	2%	1%	2%	1%	2%	1%	0%
Hemorrhage	28%	24%	13%	20%	12%	15%	48%	55%	5%	6%
Pulmonary embolism	4%	5%	2%	0%	6%	15%	1%	2%	1%	4%

2.3. Anti-VEGF Agents in Renal Cell Carcinoma

2.3.1 **Bevacizumab (Avastin®)**

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human VEGF in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. For additional updated information beyond that listed below, please refer to the bevacizumab (Avastin®) complete prescribing information (package insert).

Clinical Studies in RCC

Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing bevacizumab plus interferon alfa 2a (IFN- α2a) versus placebo plus IFN-α2a (Escudier et al. 2007b). A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either bevacizumab (10 mg/kg IV infusion every 2 weeks; n = 327) or placebo (IV every 2 weeks; n = 322) in combination with IFN-α2a (9 MIU subcutaneously three times weekly, for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (range 18−82), 96% were white, and 70% were male. The study population was characterized by MKSCC scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3-5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving bevacizumab plus IFN-α2a compared to those receiving IFN-α2a alone; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the bevacizumab plus IFN-α2a arm and 21 months in the IFN-α2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

Safety Profile

In the phase III trial of bevacizumab plus interferon α2a (Escudier et al. 2007b), grade 3−5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving IFN-α plus bevacizumab compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and

hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Grade 1−5 adverse events occurring at a higher incidence (≥ 5%) in patients receiving IFN-α plus bevacizumab compared to the IFN-α plus placebo arm are presented in the following table.

MedDRA version 10.1 term	IFN-α + Placebo (n=304)	IFN-α + bevacizumab (n=337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

2.3.2 **Pazopanib (Votrient™)**

Pazopanib (Votrient™) is a tyrosine kinase inhibitor (TKI). Pazopanib tablets are for oral administration. Each 200 mg tablet of pazopanib (Votrient™) contains 216.7 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base. For additional updated information beyond that listed below, please refer to the pazopanib (Votrient™) complete prescribing information (package insert).

Clinical Studies in RCC

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study (Sternberg et al. 2010). Patients (N = 435) with locally advanced and/or metastatic RCC who had received either no prior therapy or one prior cytokine-based systemic therapy were randomized (2:1) to receive pazopanib 800 mg once daily or placebo once daily. The primary objective of the study was to evaluate and compare the 2 treatment arms for progression-free survival (PFS); the secondary endpoints included overall survival (OS), overall response rate (RR), and duration of response.

Of the total of 435 patients enrolled in this study, 233 patients had no prior systemic therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or IFN-α-based therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics were balanced between the pazopanib and placebo arms. The majority of patients were male (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were Asian and less than 1% were other. Forty-two percent were ECOG performance status 0 and 58% were ECOG performance status 1. All patients had clear cell histology (90%) or predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more organs involved with metastatic disease. The most common metastatic sites at baseline were lung (74%), lymph nodes (56%), bone (27%), and liver (25%). A similar proportion of patients in each arm were treatment-naïve and cytokine-pretreated. In the cytokine-pretreated subgroup, the majority (75%) had received interferon-based treatment. Similar proportions of patients in each arm had prior nephrectomy (89% and 88% for pazopanib and placebo, respectively).

The analysis of the primary endpoint PFS was based on disease assessment by independent radiological review in the entire study population. PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; $P < .0001$), the treatment-naive subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; $P < .0001$), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; $P < .001$). The objective response rate was 30% with pazopanib compared with 3% with placebo ($P < .001$). The median duration of response was longer than 1 year. Analysis of overall survival was immature.

Safety Profile

Potentially serious adverse reactions with pazopanib include hepatotoxicity, hypertension, QT prolongation and torsades de pointes, arterial thrombotic events, hemorrhagic events, and gastrointestinal perforation and fistula.

Hepatic Toxicity: In a controlled clinical study with pazopanib for the treatment of

RCC, ALT >3 X ULN was reported in 18% and 3% of the pazopanib and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received pazopanib and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on pazopanib and 2/145 (1%) on placebo.

Hypertension: In a controlled clinical study with pazopanib for the treatment of RCC, 115/290 patients (40%) receiving pazopanib compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving pazopanib compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with pazopanib because of hypertension. Pazopanib has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on pazopanib.

QT Prolongation and Torsades de Pointes: In a controlled clinical study with pazopanib, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with pazopanib compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with pazopanib in the RCC studies.

Arterial Thrombotic Events: In a controlled clinical study with pazopanib, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with pazopanib compared to the placebo arm (0/145 for each event).

Hemorrhagic Events: In a controlled clinical study with pazopanib, 37/290 patients (13%) treated with pazopanib and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with pazopanib were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with pazopanib who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with pazopanib died from hemorrhage compared with no (0/145) (0%) patients on placebo. In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with pazopanib.

Hypothyroidism: In a controlled clinical study with pazopanib, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in pazopanib compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with pazopanib and no patients (0%)

in the placebo arm.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity.

Proteinuria: In the controlled clinical study with pazopanib, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with pazopanib. In 2 patients, proteinuria led to discontinuation of treatment with pazopanib.

Lipase Elevations: In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of pazopanib, clinical pancreatitis was observed in 4/586 patients (<1%).

Cardiac Dysfunction: Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

2.3.3 **Sorafenib (Nexavar®)**

Sorafenib (Nexavar®) is a multi-kinase inhibitor. Sorafenib tablets are for oral administration. Each red, round sorafenib (Nexavar®) film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib. For additional updated information beyond that listed below, please refer to the sorafenib (Nexavar®) complete prescribing information (package insert).

Clinical Studies in RCC

The safety and efficacy of sorafenib in the treatment of advanced renal cell carcinoma (RCC) were studied in the following two randomized controlled clinical trials.

The TARGET study was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy (Escudier et al. 2007a). Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MSKCC prognostic risk category (low or intermediate) and country and randomized to sorafenib 400 mg twice daily (N=384) or to placebo (N=385). Baseline demographics and disease characteristics were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the sorafenib and placebo groups, respectively.

The median PFS for patients randomized to sorafenib was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of

progression with sorafenib compared to placebo) was 0.44 (95% CI: 0.35, 0.55). A series of patient subsets were examined in exploratory univariate analyses of PFS. The subsets included age above or below 65 years, ECOG PS 0 or 1, MSKCC prognostic risk category, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting and time from diagnosis of less than or greater than 1.5 years. The effect of sorafenib on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (N=137; 65 patients receiving sorafenib and 72 placebo), for whom the median PFS was 172 days on sorafenib compared to 85 days on placebo.

Tumor response was determined by independent radiologic review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) sorafenib patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in sorafenib -treated patients primarily reflects the stable disease population.

At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for sorafenib than placebo with a hazard ratio (sorafenib over placebo) of 0.72. This analysis did not meet the prespecified criteria for statistical significance.

A Phase 2 randomized discontinuation trial in patients was also performed in patients with RCC (Ratain et al. 2006). The primary endpoint was the percentage of randomized patients remaining progression-free at 24 weeks. All patients received sorafenib for the first 12 weeks. Radiologic assessment was repeated at week 12. Patients with <25% change in bi-dimensional tumor measurements from baseline were randomized to sorafenib or placebo for a further 12 weeks. Patients who were randomized to placebo were permitted to cross over to open-label sorafenib upon progression. Patients with tumor shrinkage ≥25% continued sorafenib, whereas patients with tumor growth ≥25% discontinued treatment.

Two hundred and two patients with advanced RCC were enrolled into the randomized discontinuation trial, including patients who had received no prior therapy and patients with tumor histology other than clear cell carcinoma. After the initial 12 weeks of sorafenib, 79 patients with RCC continued on open-label sorafenib, and 65 patients were randomized to sorafenib or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to sorafenib (16/32, 50%) than in patients randomized to placebo (6/33, 18%) (p=0.0077). Progression-free survival was significantly longer in the sorafenib group (163 days) than in the placebo group (41 days) (p=0.0001, HR=0.29).

Safety Profile

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of sorafenib (very common 10% or greater,

common 1 to less than 10%, uncommon 0.1% to less than 1%):

Cardiovascular:
Common: congestive heart failure, myocardial ischemia and/or infarction
Uncommon: hypertensive crisis
Rare: QT prolongation

Dermatologic:
Very common: erythema
Common: exfoliative dermatitis, acne, flushing
Uncommon: folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin

Digestive:
Very common: increased lipase, increased amylase
Common: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia
Uncommon: pancreatitis, gastrointestinal reflux, gastritis, gastrointestinal perforations, cholecystitis, cholangitis

Note that elevations in lipase are very common (41%); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values.

General Disorders:
Very common: hemorrhage (including gastrointestinal & respiratory tract and uncommon cases of cerebral hemorrhage), asthenia, pain (including mouth, bone, and tumor pain)
Common: decreased appetite, influenza-like illness, pyrexia
Uncommon: infection

Hematologic:
Very common: leukopenia, lymphopenia
Common: anemia, neutropenia, thrombocytopenia
Uncommon: INR abnormal

Hypersensitivity:
Uncommon: hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional:
Very common: hypophosphatemia
Common: transient increases in transaminases
Uncommon: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism

Musculoskeletal:

Common: arthralgia, myalgia

Nervous System and Psychiatric:
Common: depression
Uncommon: tinnitus, reversible posterior leukoencephalopathy

Renal and Genitourinary:
Common: renal failure

Reproductive:
Common: erectile dysfunction
Uncommon: gynecomastia

Respiratory:
Common: hoarseness
Uncommon: rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

In addition, the following medically significant adverse reactions were uncommon during clinical trials of sorafenib: transient ischemic attack, arrhythmia, and thromboembolism. For these adverse reactions, the causal relationship to sorafenib has not been established.

2.3.4 **Sunitinib (Sutent®)**

Sunitinib (Sutent®) is an oral multi-kinase inhibitor. Sunitinib is for oral administration. Sunitinib malate (Sutent®) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients. For additional information beyond that listed below, please refer to the sunitinib (Sutent®) complete prescribing information (package insert).

Clinical Studies in RCC

Treatment-Naïve RCC
A multi-center, international randomized study comparing single-agent sunitinib with IFN-α was conducted in patients with treatment-naïve RCC (Motzer et al. 2007). The objective was to compare PFS in patients receiving sunitinib versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg sunitinib once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Patients were treated until disease progression or withdrawal from the study. The ITT population included 750 patients, 375 randomized to sunitinib and 375 randomized to IFN- α. Demographics were

comparable between the sunitinib and IFN- α groups with regard to age (59% vs. 67% <65 years for sunitinib vs. IFN- α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm). The most common site of metastases present at screening was the lung (78% vs. 80%, respectively), followed by the lymph nodes (58% vs. 53%, respectively) and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% vs. 77%, respectively).

There was a statistically significant advantage for sunitinib over IFN-α in the endpoint of PFS. In the pre-specified stratification factors of LDH (>1.5 ULN vs. ≤1.5 ULN), ECOG performance status (0 vs. 1), and prior nephrectomy (yes vs. no), the hazard ratio favored sunitinib over IFN-α. The ORR was higher in the sunitinib arm.

At the protocol-specified final analysis of OS, the median OS was 114.6 weeks for the sunitinib arm and 94.9 weeks for the IFN-α arm [HR= 0.821, 95% CI (0.673, 1.001)]. The median OS for the IFN-α arm includes 25 patients who discontinued IFN- α treatment because of disease progression and crossed over to treatment with sunitinib as well as 121 patients (32%) on the IFN-α arm who received post-study cancer treatment with sunitinib.

Cytokine-Refractory RCC
The use of single agent sunitinib in the treatment of cytokine-refractory RCC was investigated in a single-arm multi-center study. In this study, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-α alone must have received treatment for at least 28 days) (Motzer et al. 2006). All patients were required to have a histological clear-cell component. The primary endpoint was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) were enrolled. Patients received 50 mg sunitinib on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. There were 36 PRs as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). DR data is premature as only 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.

Safety Profile

The as-treated patient population for the treatment-naive RCC study included 735 patients, 375 randomized to sunitinib and 360 randomized to IFN-α (Motzer et al. 2007). The median duration of treatment was 11.1 months (range: 0.4 – 46.1) for

sunitinib treatment and 4.1 months (range: 0.1 – 45.6) for IFN- α treatment. Dose interruptions occurred in 202 patients (54%) on sunitinib and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on sunitinib and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for sunitinib and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on sunitinib versus IFN- α, respectively. Adverse events are summarized in the table below.

Adverse Reaction, n (%)	**Treatment Naïve RCC**			
	Sunitinib (n=375)		**INF-α (n=360)**	
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60(17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0	54 915)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	9 (2)	16 94)	0
Abdominal pain	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	40 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0	27 (7)	1 (<1)
GERD	47 (12)	1 (<1)	3 (1)	0
Flatulence	52 (14)	0	8 (2)	0
Oral pain	54 (14)	2 (<1)	2 (1)	0
Glossodynia	40 (11)	0	2 (1)	0
Hemorrhoids	38 (10)	0	6 (2)	0
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29)	32 (8)	3 (1)	0
Yellow skin	94 (25)	1 (<1)	0	0
Dry skin	85 (23)	1 (<1)	26 (7)	0
Hair color changes	75 (20)	0	1 (<1)	0
Alopecia	51 (14)	0	34 (9)	0
Erythema	46 (12)	2 (<1)	5 (1)	0
Pruritis	44 (12)	1 (<1)	24 (7)	1 (<1)
Neurology				
Altered taste	178 (47)	1 (<1)	54 (15)	0
Headache	86 (23)	4 (1)	69 (19)	0
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				

Adverse Reaction, n (%)	Treatment Naïve RCC			
	Sunitinib (n=375)		INF-α (n=360)	
Any	372 (99)	290 (77)	355 (99)	197 (55)
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity				
Endocrine				
Hypothyroidism	150 (40)	19 (5)	107 (30)	7 (2)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0	8 (2)	0
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0
Metabolism/Nutrition				
Anorexia	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0
Depression	40 (11)	0	51 (14)	5 (1)

2.4. Rationale

A capacity for neoangiogenesis is a fundamental property of cancer (Hanahan et al. 2000). With the clinical application of multiple inhibitors of VEGF signaling, angiogenesis is a validated therapeutic target. However, the overall clinical benefit of agents targeting VEGF has been less than what was hoped. An important mechanism of resistance to anti-VEGF therapy is the selection for or up-regulation of alternative pro-angiogenic pathways and treatments targeting these alternative angiogenic pathways are needed (Abdollahi et al. 2010; Bergers et al. 2008; Ellis et al. 2008). It is not presently known whether continued VEGF pathway inhibition is required for the clinical efficacy of alternative antiangiogenic agents. Moreover, biomarkers of sensitivity or resistance to antiangiogenic therapies are urgently needed.

The angiopoietin-Tie signaling system is an alternative vascular signaling pathway that is involved in vascular development and maintenance. Angiopoietin 1 (Ang1) and Angiopoietin 2 (Ang2) are ligands of Tie2, a receptor tyrosine kinase expressed on endothelial cells (Augustin et al. 2009). While Ang1 and Ang2 have opposing effects on the Tie2 receptor in most contexts, they both contribute to vascular homeostasis. High levels of Ang2 have been found in breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, and AML. In renal cell carcinoma (RCC), Ang2 is elevated at the time of progression on VEGF receptor (VEGFR) targeted therapy (Bullock et al. 2010). Thus, angiogenesis through the Ang/Tie system may contribute to anti-angiogenic therapy resistance in a subset of patients treated with VEGF pathway targeted agents.

In this trial, **we hypothesize that 1) inhibition of the angiopoietin-Tie pathway**

either alone or in combination with continued anti-VEGF therapy will result in tumor responses in patients with renal cell cancer who have progressed on anti-VEGF therapy and that **2) pretreatment tumor- and blood-derived biomarkers will predict resistance to continued anti-angiogenic treatment in patients who have progressed on anti-VEGF therapy.**

Bevacizumab, pazopanib, sorafenib and sunitinib are anti-VEGF agents that are indicated for the treatment of advanced renal cell cancer. This trial will evaluate AMG 386 alone or AMG 386 plus bevacizumab, pazopanib, sorafenib, or sunitinib after progression on at least one line of anti-VEGF therapy for renal cell cancer. Preliminary results of Phase 1B study of AMG 386 with sorafenib or sunitinib in advanced renal cell carcinoma were recently presented (Appleman et al. 2010). The preliminary efficacy results were encouraging with 1 complete response, 12 confirmed partial responses, and 15 patients with stable disease in the first 30 evaluable patients. Preliminary data from a randomized trial of sorafenib combined with AMG 386 or sorafenib plus placebo suggest the possibility of higher responses but not improved PFS with the combination (Rini et al. 2011). This trial will provide complementary data by evaluating AMG 386 at a higher dose and in anti-VEGF pretreated RCC patients. With this preliminary data, it has not been established whether anti-VEGF therapy enhances level of activity of AMG 386 alone, thus providing rationale for the randomization in this trial.

A major objective of this trial is to use pretreatment tumor biopsies to explore biomarkers of sensitivity and resistance to both angiopoietin inhibition and combined angiopoietin/VEGF inhibition in the renal cell cancer cohort. We hypothesize that the expression of angiogenic biomarkers will be influenced by exposure to an anti-VEGF agent and will therefore compare the expression pattern of biomarkers in the study biopsy to results obtained from archival specimens. The goal of these analyses – in addition to better understanding why tumors did or did not respond – is to identify a subset of biomarkers which can be further studied in future trials.

2.5. Correlative Studies Background

2.5.1 **Overview**

This trial design allows for the simultaneous exploration of tumor and blood based anti-angiogenic therapy resistance biomarkers as well as the effect of combined anti-angiopoietin and anti-VEGF therapy on circulating angiogenic factors. Because archival tumor specimens do not represent the tumor after exposure to and progression on a regimen containing an anti-VEGF agent, a research biopsy will be performed on all patients immediately prior to treatment in order to evaluate angiogenic biomarkers immediately (within 13 weeks) after VEGF targeted treatment. Blood sampling will be performed prior to treatment, once per cycle at the completion of the first 2 cycles, and upon progression.

Although AMG 386 targets a VEGF-independent pathway of angiogenesis, its activity may still be dependent on alternative pro-angiogenic signaling, particularly through the VEGF pathway. Therefore, markers of VEGF-pathway-mediated angiogenesis, and other complementary factors such as PDGF, FGF and IL-8, may be useful to select patients for continued anti-angiogenic therapy. Therefore, we will evaluate a) tumor-based biomarkers of resistance and sensitivity to anti-angiogenic therapy, b) compare these biomarkers between archival specimens and post-VEGF therapy failure specimens, c) evaluate the effects of angiopoietin inhibition with and without continued anti-VEGF therapy on circulating angiogenic biomarkers and d) evaluate pharmacogenetic correlates of anti-angiogenic therapy resistance and sensitivity. In each of these settings, biomarkers will be categorized into those suggestive of VEGF-pathway activity, angiopoietin-pathway activity, or of VEGF- and angiopoietin-independent angiogenesis. The goal of these analyses is to identify a subset of these biomarkers for future study should this agent or these combinations warrant further study. Our overall hypotheses are that:

(1) Tumors with evidence of active angiopoietin – Tie2 pathway expression will be sensitive to angiopoietin inhibition,
(2) Tumors with continued evidence of VEGF pathway activation after anti-VEGF therapy will be optimally inhibited by continuation of the anti-VEGF agent,
(3) Tumors with evidence of VEGF- and angiopoietin-independent angiogenesis will be resistant to AMG 386 + continued anti-VEGF therapy, and
(4) The expression of angiogenesis related genes will differ in archival and pre-treatment tumor biopsy specimens.

2.5.2 **Tumor-Based Correlative Studies**

In previous work, we used quantitative PCR on carefully microdissected tumor specimens to evaluate angiogenic gene expression levels in patients with metastatic colorectal cancer treated with bevacizumab, and suggested that elevated VEGFR2 and NRP-1 expression levels were associated with an improved overall survival (Zhang et al. 2010). As some previous research looking at tissue-based biomarkers of angiogenic resistance has suffered from the lack of validated and quantitative laboratory procedures; our use of quantitative real-time PCR allows for reproducible gene expression analyses. Up-regulation of the VEGF pathway genes may suggest that after progression on an anti-VEGF agent, continued VEGF-pathway inhibition is required to restrain continued angiogenesis. Thus we will examine the following:

- The intratumoral expression of the VEGF-pathway genes VEGF, VEGFR1, VEGFR2 and NRP-1 as markers of active VEGF-pathway mediated angiogenesis.

- The intratumoral expression of Ang1, Ang2, and Tie2 as markers of active angiopoietin-pathway mediated angiogenesis.
- Alternatively, resistance to anti-VEGF and anti-angiopoietin therapy may result from up-regulation of alternative pro-angiogenic pathways. The expression of IL-8, VCAM-1 and bFGF will be analyzed as markers of VEGF- and angiopoietin-independent angiogenesis.

Paraffin-embedded tumor blocks will be prepared from 1) archival tumor specimens and from 2) tumor biopsies from RCC patients taken at the start of this trial. Gene expression will be measured using a validated mRNA isolation and quantization method and normalized to an internal reference gene (Response Genetics, Inc.) as previously described (Vallbohmer et al. 2006). Briefly, each block will be reviewed for quality and tumor content by a board-certified pathologist. Ten μm-thick sections will be prepared from identified areas with the highest tumor concentration. If the histology is homogenous and contains more than 80% tissue of interest, the samples will be dissected from the slides using a scalpel. Laser capture microdissection will be applied to all other specimens. After mRNA isolation and cDNA synthesis, a fluorescence-based real-time detection method (Taqman, Applied Biosystems, Foster City, CA) will be used to quantitate the expression of each gene of interest and the internal reference gene (β-actin).

2.5.3 **Pharmacodynamic Correlative Studies**

In order to better understand the success or failure of AMG 386 + continued anti-VEGF therapy in individual patients, this randomized trial design allows the opportunity to compare the effects of AMG 386 monotherapy to AMG 386 + anti-VEGF therapy on VEGF-pathway, angiopoietin-Tie2 pathway, and VEGF-angiopoietin-pathway independent circulating angiogenic factors. Although not prospectively validated, a number of circulating biomarkers have been associated with the efficacy of antiangiogenic treatments (Jain et al. 2009; Jubb et al. 2010; Jubb et al. 2006). Changes in certain circulating angiogenic factors have been associated with the efficacy of VEGF targeted treatment (Hanrahan et al. 2010), and certain factors seem to rise upon progression on VEGF targeted therapy (Kopetz et al. 2010). We hypothesize that:

(1) AMG 386 will exert its anti-angiogenic effect by sequestering both Ang1 and Ang2, resulting in decreased circulating levels of Ang2.
(2) Resistance to AMG 386 + anti-VEGF therapy will be accompanied by increases (or lack of decreases) in circulating markers of VEGF- and angiopoietin-independent angiogenesis.

Circulating Ang2 and soluble Tie2 will be measured as plasma markers of angiopoietin-pathway activity. Plasma VEGF-A, and soluble VEGFR2 will be measured as markers of VEGF-mediated angiogenic activity. Levels of IL-8, PlGF, ICAM1, VCAM1, PDGFα, PDGFβ and FGFR ligands (including FGF2)

will be measured as markers of VEGF/angiopoietin-independent angiogenesis. Samples will be obtained at baseline (prior to cycle 1), prior to cycle 2, prior to cycle 3, and at progression. Plasma levels of selected markers will be performed by multiplex bead suspension array. Soluble VEGFR2 and Tie2 receptors and Ang2 will be measured by ELISA.

2.5.4 **Pharmacogenetic Correlative Studies**

We and others have shown that single nucleotide polymorphisms (SNPs) in VEGF pathway (VEGF and VEGFR2) genes and VEGF-pathway independent genes (IL-8, PlGF, ICAM-1, VCAM-1, and FGFR4) can predict the benefit of bevacizumab in ovarian cancer (Schultheis et al. 2008), breast cancer (Schneider et al. 2008), NSCLC (Zhang et al. 2009), and colorectal cancer patients (Shaye et al. 2007). There are incomplete data regarding the association of polymorphisms in Ang1, Ang2, and Tie2 with the development or treatment of malignancies, although one study did not show an association between an Ang2 polymorphism and ovarian, cervical, or endometrial cancer (Konac et al. 2007). In this trial, we will further explore these polymorphisms as predictors of efficacy of anti-angiopoietin and combined anti-angiopoietin/anti-VEGF therapy. Genomic DNA will be collected from peripheral mononuclear cells collected from each subject at the start of the trial. Polymorphisms in VEGF, VEGFR2, Ang2, IL-8, PlGF, ICAM-1, VCAM-1, and FGFR4 genes will be analyzed by polymerase chain reaction-restriction length polymorphism (PCR-RFLP) as previously described (Schneider et al. 2008; Schultheis et al. 2008; Shaye et al. 2007; Zhang et al. 2009).

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed renal cell carcinoma except medullary or collecting duct subtypes. Sarcomatoid differentiation will be allowed.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have documented radiologic or clinical progressive disease following at least one prior anti-VEGF regimen administered either as a single agent or in combination with other agents for at least 8 weeks. The prior anti-VEGF treatment regimen must have included bevacizumab, pazopanib, sorafenib or sunitinib administered not more than 12 weeks before study

entry. **Note:** Enrollment not more than 8 weeks after the last dose of anti-VEGF therapy is encouraged. Nevertheless, intercurrent therapy with an mTOR inhibitor (everolimus or temsirolimus) will be allowed if progression on that treatment is observed within 12 weeks of the prior anti-VEGF therapy.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of AMG 386 alone or in combination in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 Any number of prior regimens is allowed. Prior investigational therapy is allowed.

3.1.6 ECOG performance status ≤1 (Karnofsky ≥ 70%, see Appendix A).

3.1.7 Life expectancy of greater than 3 months.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ institutional upper limits of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– PTT or aPTT	≤ ULN per institutional laboratory range and INR ≤1.5
– creatinine	within normal institutional limits
OR	
– creatinine clearance	>40 mL/min per 24 h urine collection or calculated according to the Cockcroft-Gault formula

$$\text{CrCl (mL/min)} = \frac{\text{(140-age) x actual body weight (kg)}}{\text{72 x serum creatinine (mg/dL)}} \text{ (x 0.85 for females)}$$

– urinary protein	≤100 mg/dL in urinalysis or ≤1+ on dipstick, unless quantitative protein is <1000 mg in a 24 h urine sample

3.1.9 Generally well-controlled blood pressure with systolic blood pressure ≤140 mmHg AND diastolic blood pressure ≤90 mmHg prior to enrollment. The use of anti-hypertensive medications to control hypertension is permitted.

3.1.10 Patients must have a tumor site amenable to biopsy as determined by the treating investigator. Any questions regarding suitability of a site for biopsy will be adjudicated by the principal investigator.

3.1.11 Patients must be willing to consent to tumor biopsy for research purposes.

3.1.12 Patients should have archival tumor tissue (either unstained slides or tumor blocks) available for retrieval. See section 9.1.2 for specimen shipping instructions.

3.1.13 The effects of AMG 386 are known to be detrimental to fetal development. For this reason and because inhibitors of angiogenesis as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry,for the duration of study participation, and 6 months after completion of AMG 386. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of AMG 386 and bevacizumab, pazopanib, sunitinib, or sorafenib administration.

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

3.2. Exclusion Criteria

3.2.1 Intolerance of prior treatment with bevacizumab, pazopanib, sorafenib, or sunitinib.

Note: Subjects who required a dose reduction of pazopanib, sorafenib, or sunitinib during prior therapy MAY be eligible if they tolerated the agent after dose level reduction (to a minimum of dose level -2 as defined in this protocol; see Section 6 for dose levels).

3.2.2 Central nervous system metastases unless: (1) metastases have been treated and have remained controlled for at least two weeks following treatment, AND (2) patient has no residual neurological dysfunction off corticosteroids for at least one week. A CT or MRI to evaluate for CNS disease is required for symptomatic patients only.

3.2.3 History of venous or arterial thromboembolism within 12 months prior to enrollment/randomization.

3.2.4 History of clinically significant bleeding within 6 months of enrollment/randomization.

3.2.5 Unresolved toxicities from prior systemic therapy that are CTCAE version 3.0

or 4.0 ≥ Grade 2 in severity except alopecia.

3.2.6 Currently or previously treated with AMG 386, or other molecules that inhibit the angiopoietins or Tie2 receptor.

3.2.7 Clinically significant cardiovascular disease within 12 months prior to enrollment/randomization, including myocardial infarction, unstable angina, grade 2 or greater peripheral vascular disease, cerebrovascular accident, transient ischemic attack, congestive heart failure, or arrhythmias not controlled by outpatient medication or placement of percutaneous transluminal coronary angioplasty/stent.

3.2.8 Major surgery within 28 days prior to enrollment or still recovering from prior surgery.

3.2.9 Minor surgical procedures **except** placement of tunneled central venous access device within 3 days prior to enrollment.

3.2.10 Non-healing wound, ulcer (including gastrointestinal), or fracture.

3.2.11 Subject not consenting to the use of highly effective contraceptive precautions (*e.g.*, double barrier method [*i.e.*, condom plus diaphragm]) during the course of the study and for 6 months after administration of the last study medication.

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AMG 386 or the anti-VEGF agent used in study.

3.2.13 History of allergic reactions to bacterially-produced proteins.

3.2.14 Patients who have had anti-VEGFR tyrosine kinase inhibitor within 1 week, mTOR inhibitor within 1 week or anti-VEGF antibody therapy within 3 weeks prior to entering the study. Patients who have had other forms of chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.15 Patients who have not yet completed at least 21 days (30 days for prior monoclonal antibody therapy) since ending other investigational device or drug trials, or who are currently receiving other investigational treatments.

3.2.16 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP450 3A4 are ineligible due to the potential for interaction with pazopoanib, sorafenib, or sunitinib. Caution is advised for patients requiring weak or moderate CYP450 3A4 inhibitors or inducers. Specifically prohibited medicines include indinavir, nelfinavir, ritonavir, clarithromycin,

itraconazole, ketoconazole, nefazodone, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, and troglitazone.

Note: A list of CYP450 3A4 inhibitors and inducers is included in Appendix C. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.asp; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.17 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.18 Pregnant women are excluded from this study because AMG 386, bevacizumab, pazopanib, sorafenib, and sunitinib are inhibitors of angiogenesis with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AMG 386, breastfeeding **must** be discontinued if the mother is treated with AMG 386.

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

3.2.20 Inability to take oral medications on a continuous basis. Patients who are to take pazopanib, sorafenib, or sunitinib and are unable to swallow pills whole are ineligible (The pills cannot be crushed or broken).

3.2.21 Any condition which in the investigator's opinion makes the subject unsuitable for study participation

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. The anticipated accrual in ethnicity/race and gender categories is provided below:

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	8	9	17
Not Hispanic or Latino	17	44	61
Ethnic Category: Total	25	53	78
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	2	4	6
Black or African American	2	8	10
Native Hawaiian or other Pacific Islander	0	0	0
White	21	41	62
Racial Category: Total	25	53	78

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the California Cancer Consortium Data Coordinating Center at the City of Hope. All sites should call the Data Coordinating Center at (626) 256-4673 extension 65928 to verify study status.

Following registration, patients should be scheduled for a research biopsy within 7 days. Treatment should be initiated between 3 and 5 working days after the biopsy pending full recovery from any biopsy related effects. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Each participating institution will order DCTD-supplied agents directly from CTEP, DCTD. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the City of Hope Data Coordinating Center (DCC) FAX (626-256-8654).

4.2. Registration Process

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the Consortium office (Data Coordinating Center for the California Cancer Consortium) at the City of Hope (626-256-4673, ext. 65928), FAX a copy of the completed eligibility checklist, required pre-study tests (laboratory and pathology report), signed Informed Consent, signed Patients' Bill of

Rights and HIPAA authorization form. (FAX Number: 626-256-8654). **See Appendix G ("Registration Procedures")**.

The research nurse or data manager at the participating site will then call the Data Coordinating Center at Tel# 626-256-4673 extension 65928 to confirm receipt of all registration documents. To complete the registration process, the data coordinating center coordinator will:

• Verify the eligibility
• Register the patient on study
• Assign a patient accession number
• Fax or e-mail the patient study number and dose to the participating site
• Call the research nurse or data manager at the participating site and verbally confirm registration.

4.3. Randomization Process

Statisticians in the Data Coordinating Center will prepare a stratified randomization list of treatment assignments, with stratification by participating institution. This process will utilize a random permuted block design, so as to minimize the difference in the number of patients assigned to the 2 treatment arms for any given institution. The block sizes will be chosen by the Study Biostatistician, and not revealed until patient accrual has been completed.

The stratified randomization list will be provided to the Study Coordinator, who will be the only other person with access to the list. It will allow for instant determination of (randomized) treatment assignment for the patient, as soon as his eligibility has been confirmed.

If an additional institution(s) later join(s) the study, an additional stratified randomization list(s) will be prepared in a similar manner to accommodate the patients to be registered and randomized from that new institution(s).

5. TREATMENT PLAN

5.1. Pre-Treatment Tumor Biopsy

Assent to performing a fresh tumor biopsy is a requirement of this trial. At the time of enrollment, the treating investigator will select a site amenable for tumor biopsy. The biopsy should be performed in the first 7 days after registration. The tumor site used for biopsy may be modified in consultation with appropriate specialists (e.g. radiologist, interventional radiologist). If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and appropriate specialists, a biopsy will be attempted. The use of imaging to facilitate biopsies will be decided by appropriately trained specialists and may include an

ultrasound (US), a computer tomography (CT) scan, or a magnetic resonance imaging (MRI) scan. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and appropriate specialists.

Biopsy will be performed by a qualified professional. It is preferred that a core biopsy system be used to obtain at least 2 core biopsies not less than 20 gauge in diameter and 1 cm in length. Tumor biopsies will be obtained with the help of the Interventional Radiology team by a percutaneous approach. When necessary for clinical management, one biopsy sample will be sent for pathological review and the remainder will be sent for correlative studies; if only a single biopsy is feasible, then the sample will be divided. If not necessary for clinical management, the entire specimen will be sent for correlative studies after processing.

5.2. Agent Administration

Treatment will be administered on an outpatient basis. The first cycle of treatment should begin 3-5 working days after the biopsy procedure when feasible and is subject to full recovery from any biopsy related complications, and should also begin at least 14 days from the last dose of an mTOR inhibitor if the patient was previously treated with an mTOR inhibitor. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Those randomized to Arm A will receive AMG 386 monotherapy and those randomized to Arm B will receive AMG 386 plus their prior anti-VEGF agent as described in the tables below.

REGIMEN DESCRIPTION FOR ARM A (AMG 386 Monotherapy)					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
AMG 386	Flush the IV line with 0.9% NS (minimum volume is 5 mL) before and after the each IV infusion.	15 mg/kg	IV over 60 minutes[a]	Day 1, 8, 15, 22, 29, and 36	42 days (6 weeks)
[a] If the first infusion is well tolerated, subsequent infusions may be delivered over 30 minutes.					

REGIMEN DESCRIPTION FOR ARM B (AMG 386 + continued anti-VEGF therapy)					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
AMG 386	Flush the IV line with 0.9% NS (minimum volume is 5 mL) before and after the each IV infusion.	15 mg/kg	IV over 60 minutes[a]	Day 1, 8, 15, 22, 29, and 36	42 days (6 weeks)
ONE of the following anti-VEGF agents will be administered:					
Bevacizumab	Dilute in 100 mL 0.9% Sodium Chloride Injection, USP	10 mg/kg	IV over 90 minutes[b]	Day 1, 15, and 29	42 days (6 weeks)
Pazopanib	At least 1 hour before or 2 hours after a meal	800 mg once daily[d]	Oral[c]	Daily, Days 1-42	
Sorafenib	At least 1 hour before or 2 hours after a meal	400 mg BID[d]	Oral[c]	Daily, Days 1-42	42 days (6 weeks)
Sunitinib	With or without food	50 mg once daily[d]	Oral[c]	Daily, Days 1-28	

[a] If the first infusion is well tolerated, subsequent infusions may be delivered over 30 minutes.
[b] Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.
[c] The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.
[d] The standard starting dose is given. Patients may start at a lower dose based on toxicity during prior administration. See section 6 for dose levels.

5.2.1 **AMG 386**

The actual dose of AMG 386 will be based upon the subject's actual weight (Kg). Baseline weight of a subject should be taken prior to the first dose of AMG 386, and subsequent weights will be taken on Day 1 of each cycle. Currently, the 240 mg vials are being used in all CTEP sponsored protocols. Once the NCI has depleted the 240 mg supply, stop using the dosing table that is currently available in the protocol. All calculated dose in Dose Levels 10mg/kg, 15 mg/kg, and 30 mg/kg will be rounded to the nearest vial size using 150 mg or/and 600 mg vials. Please refer to Appendix H for dose rounding guidelines that use the 150 mg and

600 mg vials.

Subject's actual weight	AMG 15 mg/kg
Weight in kilograms (kg)	AMG 386 dose in milligrams (mg)
35 to 44.9	600 mg
45 to 54.9	750 mg
55 to 64.9	900 mg
65 to 74.9	1050 mg
75 to 84.9	1200 mg
85 to 94.9	1350 mg
95 to 104.9	1500 mg
105 kg and above	Add 150 mg AMG 386 for each additional 10 kg in subject's weight

Every effort should be made to keep the weekly AMG 386 infusions exactly 7 days apart; however, occasionally a weekly dose may need to be given off schedule due to logistical reasons. Appropriate documentation of AMG 386 dosing must be maintained in the source documents and Case Report Form.

A physician or medical staff involved in study evaluations must be available during the administration of investigational product to assess and treat adverse events that may arise during dosing. Subjects will be monitored in the clinic for at least 1 hour after the completion of AMG 386 infusions for any signs of adverse events for the first dose of therapy. For all subsequent dosing, subjects will be monitored for at least 30 minutes after the completion of AMG 386.

The first dose of AMG 386 will be administered as an IV infusion using an intravenous infusion pump given over a 60-minute period. Administration of AMG 386 by methods other than infusion pump must be discussed and approved by the sponsor prior to administration. If the initial dose administration is well tolerated, future administrations of AMG 386 may be given in no less than 30 minutes at the discretion of the investigator.

Before and after each IV infusion, the IV access will be flushed with a minimum of 5.0 mL of sterile 0.9% NaCl suitable for injection. AMG 386 may be given through a peripheral IV or through a central catheter (including but not limited to a port-a-cath, Hickman, triple lumen catheter, or PICC line). Subjects must be monitored throughout and immediately after the administration of AMG 386. If AMG 386 extravasates during IV administration, the infusion must be immediately stopped. There is no specific treatment for extravasation of AMG 386. Supportive care may be given as per institutional policy and guidelines. The subject may also develop a reddened area around the site of infiltration which is caused by accumulation of investigational product in the surrounding tissues

(depot effect). If this occurs, tell patients to report it to the healthcare research team. The remaining volume of AMG 386 may be administered through a separate IV well away from the area of extravasation (or the opposite arm).

5.2.2 **Bevacizumab**

Bevacizumab will be administered as an intravenous infusion on Day 1, 15, and 29 in a 42-day Cycle. Bevacizumab should be administered after AMG 386 on the days when these two drugs are both administered. The initial dose on this trial should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

5.2.3 **Pazopanib**

Pazopanib is supplied as 200 mg tablets. The initial dose of pazopanib for this trial is 800 mg (4 tablets) orally once daily without a scheduled off-treatment period. The dose of pazopanib should not exceed 800 mg per day at any point on this trial. Patients who required a dose reduction to 400 mg orally once daily or 200 mg orally once daily due to toxicity during prior treatment with pazopanib will be treated with that dose. A lower starting dose is not allowed. Because specific safety data for the combination of pazopanib and AMG 386 is not available, extra caution will be applied to the first 5 patients receiving this combination. Toxicity experienced by these 5 patients will be reviewed on monthly CCCP conference calls.

Exposure is increased when pazopanib is taken with food. Therefore, pazopanib should be taken without food (at least 1 hour before or 2 hours after a meal).

Pharmacokinetic results indicate that the bioavailability and the rate of absorption of pazopanib are increased after administration of the crushed tablet relative to administration of the whole tablet. Do not crush tablets due to the potential for increased rate of absorption that may affect systemic exposure.

The patient will be requested to maintain a medication diary (see Appendix E) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. Patients will be instructed to record doses as they take them (and not to batch entries at a later time) and how to correct errors if they occur.

5.2.4 **Sorafenib**

Sorafenib is supplied as 200 mg tablets. The initial dose of sorafenib for this trial

is 400 mg (2 tablets) orally twice a day without a scheduled off-treatment period. The dose of sorafenib should not exceed 800 mg per day at any point on this trial. Patients who required a dose reduction to 400 mg daily or 400 mg every other day due to toxicity during prior treatment with sorafenib will be treated with those doses. A lower starting dose is not allowed.

The bioavailability is reduced when sorafenib is taken with a fatty meal. Therefore, sorafenib should be taken twice daily without food (at least 1 hour before or 2 hours after a meal).

The patient will be requested to swallow tablets whole (to not chew or crush the tablets) and maintain a medication diary (see Appendix E) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. Patients will be instructed to record doses as they take them (and not to batch entries at a later time) and how to correct errors if they occur.

5.2.5 **Sunitinib**

Sunitinib is supplied as 50 mg, 25 mg, and 12.5 mg capsules. The initial dose of sunitinib on this trial is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. The dose of sunitinib should not exceed 50 mg per day at any point on this trial. Patients who required a dose reduction to a dose of 37.5 mg or 25 mg due to toxicity during prior treatment with sunitinib will be treated with that dose daily for 4 weeks followed by two weeks off treatment. A lower starting dose is not allowed.

Food has no effect on the bioavailability of sunitinib. Therefore, sunitinib can be taken with or without food.

There may be a yellow discoloration of the skin area following direct contact with the capsules. Patients should wash the exposed area with soap and water immediately.

The patient will be requested to maintain a medication diary (see Appendix E) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. Patients will be instructed to record doses as they take them (and not to batch entries at a later time) and how to correct errors if they occur.

5.3. General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of pazopanib, sorafenib and sunitinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agents.

Blood pressure should be assessed at least once every 3 weeks for patients receiving bevacizumab, pazopanib, sorafenib, or sunitinib. More frequent monitoring may be appropriate for patients with a history of elevated blood pressure while taking anti-VEGF agents and should follow institutional guidelines. High blood pressure may require initiation or increase in hypertensive medication according to routine practice. Treatment modifications due to hypertension should follow instructions in Section 6.6. Patients should not take grapefruit/grapefruit juice while receiving pazopanib, sorafenib, or sunitinib. Supportive care for symptoms related to anti-VEGF agents not explicitly defined in this protocol should follow institutional protocol and guidelines.

5.4. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Treatment delay of greater than 4 weeks for any reason,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5. Duration of Follow Up

Patients will be followed for approximately 4-8 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1. AMG 386 Dose Modification

Toxicity will be graded according to CTCAE version 4.0 until March 31, 2018, except edema/lymphedema. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. There will be no dose reductions for AMG 386.

A special note on Edema/Lymphedema: A higher incidence of peripheral edema has been associated with AMG 386. To provide a common framework for reporting edema (including lymphedema), investigators should report edema and manage their subjects as **defined in this section**.

All AEs of edema/lymphedema must be reported and graded as found in this section and *NOT* per CTCAE v5.0.

Investigators should attempt to ascertain the etiology of edema, which may include, but is not limited to, tumor obstruction of lymphatic or blood vessels, congestive heart failure, iatrogenic fluid overload, renal insufficiency, nephritic syndrome, or other significant hypoalbuminemic states.

- **Reporting of Edema/Lymphedema:** Edema should be classified, graded, and reported on the adverse event eCRF as follows:

  1. **Classify the extent** of edema:
     - LOCALIZED (confined to a single body area, e.g., lower extremities only), or
     - GENERALIZED (extending to more than a single body area)

  2. **Grade the AE** (whether localized or generalized edema/lymphedema) **as follows**:

Edema/Lymphedema (grade based on this table, NOT per CTCAE v5.0)	**Grade 1 (MILD)**	Trace thickening or faint discoloration of the affected area
	Grade 2 (MODERATE)	Marked discoloration; leathery skin texture; papillary formation
	Grade 3 (SEVERE)	Severe symptoms that may involve skin blistering or skin breakdown; limitations to activities of daily living (ADL)
Edema of a **visceral organ or body cavity** (such as pulmonary congestion, ascites, or pleural effusion): grading based on CTCAE v5.0 but NOT per this section.		

- **Pleural Effusion and Ascites**: Since AMG 386 is known to cause or worsen pre-existing pleural effusions and ascites, these adverse events should be managed as in the table of AMG 386 dose modification guidelines below.

NOTE: Each invasive procedure required for interventional treatment of pleural effusion or ascites should be documented on the appropriate eCRFs.

In subjects without a documented history of malignant pleural effusion or ascites, investigators should attempt to exclude disease progression as the cause of any new onset, or substantially worsening ascites or pleural effusion. In some settings, cytology of aspirated fluid may help in this determination (RECIST v1.1, cytology and histology section).

Dose modification of AMG 386 for edema and other AEs should follow the table below:

<table>
<tr><th colspan="3">Treatment Modification for AMG 386-Related Adverse Events (Based on CTCAE v4.0)</th></tr>
<tr><th>Event</th><th>CTCAE v4 Grade (unless noted otherwise)</th><th>Action to be Taken</th></tr>
<tr><td colspan="3">• In the event that AMG 386 is held for >28 days due to treatment-related toxicity or any other reasons, AMG 386 will be permanently discontinued.
• AMG 386 may be held for a maximum of 2 times for treatment-related toxicity. If AMG 386 needs to be held for treatment-related toxicity for a third time, AMG 386 will be permanently discontinued.</td></tr>
<tr><td rowspan="4">Edema/lymphedema:</td><td colspan="2">Edema should be classified and graded as per instructions above</td></tr>
<tr><td>Grade 1:
(Trace thickening or faint discoloration of the affected area)</td><td>Continue AMG 386 dosing per protocol and treat per institutional guidelines.</td></tr>
<tr><td>Grade 2:
(Marked discoloration; leathery skin texture; papillary formation)</td><td>Continue AMG 386 dosing per protocol and treat per institutional guidelines.</td></tr>
<tr><td>Grade 3:
[(Severe symptoms that may involve skin blistering or skin breakdown; limitations to activities of daily living (ADL)]</td><td>Discontinue AMG 386 permanently. Treat edema/lymphedema per institutional guidelines.</td></tr>
<tr><td>Pleural effusion and ascites:</td><td colspan="2">Investigators should document each paracentesis and/or thoracentesis for pleural effusion or ascites that occurs while a subject is on study.</td></tr>
</table>

Treatment Modification for AMG 386-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade (unless noted otherwise)**	**Action to be Taken**
	Non-life-threatening	• Treat per institutional guidelines which may include: non-investigational diuretics, thoracentesis, chest tube drainage, paracentesis or pleurodesis • If chest tube drainage or pleurodesis is required, AMG 386 should be held until at least two days after chest tube removal and the patient's condition is stable. • If AMG 386 is interrupted more than two times or beyond 28 days for pleural effusion/ascites, but continuation of AMG386 is clinically warranted, consultation with the study chair and sponsor (CTEP) is required before resuming AMG386
	Life-threatening	Institute emergency measures per institutional guidelines. Permanently discontinue AMG 386.
Hemorrhage (CNS):	Any grade	Permanently discontinue AMG 386.
Hemorrhage:	≥ Grade 3	Permanently discontinue AMG 386.
Arterial thromboembolic event (CVA, myocardial ischemia or infarction, arterial thrombosis):	Any grade	Permanently discontinue AMG 386.
Venous thromboembolic events:	Grade 1 or 2	Continue AMG 386. Subjects who, while on anticoagulation, develop a second venous thromboembolic event of Grade 2 or higher, should permanently discontinue AMG 386.
	Grade 3 or asymptomatic Grade 4	Hold AMG 386. • If the planned duration of the full-dose anticoagulant is ≤2 weeks, AMG 386 should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is >2 weeks, AMG 386 may be resumed (at the same dose) during the period of full-dose anticoagulation if the following criterion is met: the subject must have an in-range INR (usually between 2 and 3) on a stable dose of a coumarin-type anticoagulant OR at least 1 week of therapy on a low molecular weight heparin (or similar non-coumarin-type anticoagulant) prior to restarting AMG 386. If VTE recurred or worsened on anti-coagulation: discontinue AMG 386.
	Symptomatic Grade 4 VTE	Discontinue AMG 386.

Treatment Modification for AMG 386-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade (unless noted otherwise)**	**Action to be Taken**
Infusion reactions and delayed infusion-related reactions:	*Any potential infusion reaction should be classified based upon severity and time of onset relative to the infusion and reported as an infusion reaction and the underlying symptoms on the AE CRF.* *NOTE: infusional reactions usually occur during or within 24 hours of the drug administration. If infusional reactions are suspected more than 24 hours after the dosing of AMG 386, the patients should be treated as per institutional guidelines and decision on subsequent treatment should be discussed with the study chair.	
	Mild or moderate	Temporally hold AMG386, and treat per institutional guidelines. AMG 386 dosing may resume; however, all subsequent doses of AMG 386 should be administered no faster than over 60 minutes.
	Severe or life-threatening	Treat per institutional guidelines. Discontinue AMG386.
Hypokalemia:	Subjects should have their serum potassium checked and managed as per local medical practice. If hypokalemia is present, replacement should be managed with either oral and/or parenteral replacement, according to institutional practice and to the degree of hypokalemia present. It is recommended that the subject's serum potassium level should be maintained within the normal range, as much as possible, during study treatment.	
Other attributable toxicities not specified:	Grade 3	When a subject experiences a grade 3 toxicity considered to be related to AMG 386, AMG386 will be held until the toxicity resolves to ≤ grade 1 or the subject's baseline.
Other attributable toxicities not specified:	Grade 4	If a grade 4 event is considered to be related to AMG386, the study should be discontinued. Resuming AMG386 may be considered in patients who have shown benefit from the protocol and the toxicities have resolved to < grade 2, however, approval by the study chair and the sponsor is required.

6.2. Bevacizumab Dose Modification

There will be no dose reductions for bevacizumab, only dose delays. If delay is required, bevacizumab should resume at the same dose. Please see section 6.6 for dose modification for hypertension and proteinuria.

Dose modification of bevacizumab should follow the table below:

Treatment Modification for Bevacizumab-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade**	**Action to be Taken**
Allergic reactions, or Acute infusional reactions:	Grade 1-2	Premeds should be given with the next dose, and infusion time must not be reduced for the subsequent infusion.
	≥ Grade 3	Discontinue bevacizumab.
Arterial Thrombotic Event:	Any grade	Discontinue bevacizumab.

Treatment Modification for Bevacizumab-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade**	**Action to be Taken**
Reversible Posterior Leukoencephalopathy Syndrome:	Any grade	Discontinue bevacizumab.
Acute Venous Thrombosis:	Grade 1 or 2	Continue bevacizumab. Subjects who develop a second venous thromboembolic event of Grade 2 or higher while on anticoagulation should permanently discontinue bevacizumab.
	Grade 3 or asymptomatic Grade 4	Hold bevacizumab. • If the planned duration of the full-dose anticoagulant is ≤2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed (at the same dose) during the period of full-dose anticoagulation if the following criterion is met: the subject must have an in-range INR (usually between 2 and 3) on a stable dose of a coumarin-type anticoagulant OR at least 1 week of therapy on a low molecular weight heparin (or similar non-coumarin-type anticoagulant) prior to restarting bevacizumab. If VTE recurred or worsened on anti-coagulation: discontinue bevacizumab.
	Symptomatic Grade 4 VTE	Discontinue bevacizumab.
Wound dehiscence requiring medical or surgical intervention:	Any grade	Discontinue bevacizumab.
GI perforation, GI leak or fistula:	Any grade	Discontinue bevacizumab.
Hemoptysis:	≥ Grade 2	Discontinue bevacizumab.
Hemorrhage (CNS):	Any grade	Discontinue bevacizumab.
Hemorrhage:	≥ Grade 3	Discontinue bevacizumab.
Other attributable toxicities not specified:	Grade 3	Hold bevacizumab for up to 4 weeks until symptoms resolve to ≤ Grade 1.
Other attributable toxicities not specified:	Grade 4	If a grade 4 event is considered to be related to bevacizumab, the study should be discontinued. Resuming bevacizumab may be considered in patients who have shown benefit from the protocol and the toxicities have resolved to < grade 2, however, approval by the study chair is required.

6.3. Pazopanib Dose Modification

For patients treated initially with 800 mg pazopanib daily, the initial dose reduction should be to 400 mg, and additional dose decrease should be in 200 mg steps based on individual tolerability. For patients treated initially with 400 mg daily one dose reduction to 200 mg is allowed based on individual tolerability. The minimum daily dose of

pazopanib is 200 mg daily and the dose of pazopanib should not exceed 800 mg. Please see section 6.6 for dose modification for hypertension and proteinuria. Dose modification of pazopanib for other toxicities should follow the tables below.

Pazopanib Dose Levels	
Dose Level	**Pazopanib Dose**
1	800 mg (4 tablets) orally daily
-1	400 mg (2 tablets) orally daily
-2	200 mg (1 tablet) orally daily

Treatment Modification for Pazopanib-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade**	**Action to be Taken**
Other attributable toxicities not specified:	Grade 3	Hold pazopanib for up to 4 weeks until symptoms resolve to ≤ Grade 1.
Other attributable toxicities not specified:	Grade 4	If a grade 4 event is considered to be related to pazopanib, the study should be discontinued. Resuming pazopanib may be considered in patients who have shown benefit from the protocol and the toxicities have resolved to < grade 2, however, approval by the study chair is required.

6.4. Sorafenib Dose Modification

For those treated with 800 mg sorafenib daily, the initial dose reduction should be to 400 mg. For patients treated initially with 400 mg daily one dose reduction to 400 mg every other day is allowed based on individual tolerability. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib. Please see section 6.6 for dose modification for hypertension and proteinuria. Dose modification of sorafenib for other toxicities should follow the tables below.

Sorafenib Dose Levels	
Dose Level	**Sorafenib Dose**
1	400 mg (2 tablets) orally twice daily
-1	400 mg (2 tablets) orally once daily
-2	400 mg (2 tablets) orally once every other day

Treatment Modification for Sorafenib -Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade (unless noted otherwise)**	**Action to be Taken**

Treatment Modification for Sorafenib -Related Adverse Events (Based on CTCAE v4.0)			
Event	**CTCAE v4 Grade (unless noted otherwise)**	**Action to be Taken**	
Skin Toxicity:	Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patients normal activity	Any occurrence	Institute supportive measures immediately and continue sorafenib treatment.
	Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Institute supportive measures immediately and continue sorafenib treatment. If no improvement in 7 days, see below.
		No improvement in 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment for a minimum of 7 days, until toxicity has resolved to grade 0–1. When resuming treatment after dose interruption, resume sorafenib at a reduced dose level.
		4th occurrence	Discontinue sorafenib.
	Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment for a minimum of 7 days, until toxicity has resolved to grade 0–1. When resuming treatment after dose interruption, resume sorafenib at a reduced dose level.
		3rd occurrence	Discontinue sorafenib.
Other attributable toxicities not specified:	Grade 3	Hold pazopanib for up to 4 weeks until symptoms resolve to ≤ Grade 1.	
Other attributable toxicities not specified:	Grade 4	If a grade 4 event is considered to be related to sorafenib, the study should be discontinued. Resuming sorafenib may be considered in patients who have shown benefit from the protocol and the toxicities have resolved to < grade 2, however, approval by the study chair is required.	

6.5. Sunitinib Dose Modification

Dose interruption and/or dose modification of sunitinib in 12.5 mg decrements is recommended based on individual safety and tolerability. Please see section 6.6 for dose modification for hypertension and proteinuria. Dose modification of sunitinib for other toxicities should follow the tables below.

Sunitinib Dose Levels	
Dose Level	**Sunitinib Dose**
1	50 mg orally daily 4 weeks on, followed by 2 weeks off
-1	37.5 mg orally daily 4 weeks on, followed by 2 weeks off
-2	25 mg orally daily 4 weeks on, followed by 2 weeks off

Treatment Modification for Sunitinib-Related Adverse Events (Based on CTCAE v4.0)		
Event	**CTCAE v4 Grade**	**Action to be Taken**
Other attributable toxicities not specified:	Grade 3	Hold sunitinib for up to 4 weeks until symptoms resolve to ≤ Grade 1.
Other attributable toxicities not specified:	Grade 4	If a grade 4 event is considered to be related to sunitinib, the study should be discontinued. Resuming sunitinib may be considered in patients who have shown benefit from the protocol and the toxicities have resolved to < grade 2, however, approval by the study chair is required.

6.6. Management of Hypertension and Proteinuria

Dose modification guidelines for AMG 386 are listed in Section 6.1. Below are dose modification tables for bevacizumab, pazopanib, sorafenib, and sunitinib for the following adverse events: hypertension and proteinuria. Blood pressure should be measured at least once every 3 weeks for patients receiving bevacizumab, pazopanib, sorafenib, or sunitinib. If a new anti-hypertensive is to be added, the choice of drug is at the discretion of treating physician. Based on prior experience, vasodilators such as dihydropyridine calcium channel blockers, angiotensin blockers, and alpha-blockers are recommended agents.

Treatment Modification for Hypertension (Based on CTCAE v4.0)		
CTCAE v4 Grade	**Occurrence**	**Action to be Taken**
Grade 1	Any occurrence	No dose modification is required.
Grade 2	Any occurrence	The dose of bevacizumab, pazopanib, sorafenib, or sunitinib should be held for resting SBP > 150 or resting DBP > 90 at the time of treatment. Dose should also be held for symptomatic hypertension regardless of grade or blood pressure level. Dose may be held for up to 4 weeks. Initiate anti-hypertensive therapy if patient not on any antihypertensive agent. Ideal goal for blood pressure is < 140/80.
Grade 3	1st occurrence	Hold bevacizumab, pazopanib, sorafenib, or sunitinib. Medications should be used or added for blood pressure control. Ideal goal for blood pressure is < 140/80. Resume treatment at the same dose when blood pressure controlled to < grade 2.
	2nd or higher occurrence	Hold bevacizumab, pazopanib, sorafenib, or sunitinib. Medications should be used or added for blood pressure control. Ideal goal for blood pressure is < 140/80. Resume treatment with a one-level dose reduction of pazopanib, sorafenib, or

Treatment Modification for Hypertension (Based on CTCAE v4.0)		
CTCAE v4 Grade	**Occurrence**	**Action to be Taken**
		sunitinib when blood pressure controlled to < grade 2 (the dose of bevacizumab is not modified). If HTN cannot be controlled with medications, remove patient from protocol treatment.
Grade 4		Remove patient from protocol treatment

Treatment Modification for Proteinuria	
Proteinuria	**Action to be Taken**
Urine dipstick < 2+ protein	No action.
Urine dipstick ≥ 2+ protein	Collect 24 hour collection for protein and creatinine. If < 3.5 gm, continue to monitor 24-hour urine collection each cycle.
24-hour urine collection ≥ 3.5gm	Hold bevacizumab, pazopanib, sorafenib, or sunitinib and repeat 24-hour collection in 2 weeks. Resume treatment if < 3.5 gm. Discontinue bevacizumab, pazopanib, sorafenib, or sunitinib if drug held more than 4 weeks.
Grade 4 or nephrotic syndrome	Discontinue bevacizumab, pazopanib, sorafenib, or sunitinib.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1. Comprehensive Adverse Events and Potential Risks Lists (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf* for further clarification. *Frequency is provided based on 1556 patients.* Below is the CAEPR for AMG 386 (trebananib).

NOTE:

- Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs,

use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPR for AMG 386 (trebananib, NSC 751173)

Version 2.6, June 4, 2018[1]

Adverse Events with Possible Relationship to AMG 386 (Trebananib) (CTCAE 5.0 Term) [n= 1556]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
		Myocardial infarction[2]	
EYE DISORDERS			
		Blurred vision	
		Eye disorders - Other (retinal vascular thrombosis) [2,3]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
		Ascites	
	Diarrhea[2]		***Diarrhea[2] (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face[2]		***Edema face[2] (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue[2]		***Fatigue[2] (Gr 3)***
	Pain		***Pain (Gr 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		***Allergic reaction[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[2,4]		***Infusion related reaction[2,4] (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hypokalemia		
RENAL AND URINARY DISORDERS			
	Proteinuria[2]		***Proteinuria[2] (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pleural effusion	
		Respiratory failure[2]	
VASCULAR DISORDERS			
		Hemorrhage[5]	
	Hypertension		
		Thromboembolic event[3]	

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

[2]These adverse events attributable to AMG 386 (trebaninib) have been reported primarily in studies of AMG 386 (trebaninib) in combination with VEGF- and/or tyrosine kinase-inhibitors

and/or with chemotherapy. Retinal vascular thrombosis (arterial or venous) may result in permanent impairment of vision.

[3]Thromboembolic events, including Cerebral venous thrombosis, Jugular vein thrombosis, Peripheral artery thrombosis, Subclavian vein thrombosis, Deep vein thrombosis, Pulmonary embolism, Retinal vascular thrombosis, and Intracardiac thrombus have been observed in AMG 386 (trebananib) trials.

[4]Symptoms of allergic reactions and/or infusion related reactions may include Fever, Chills, Headache, Rash, Flushing, Swelling, and Shortness of breath. Severe allergic reactions can cause Dizziness, Hypotension, or Difficulty swallowing and may be life-threatening.

[5]Hemorrhage events, some of which may be serious, including Cerebral hemorrhage, Esophageal varices hemorrhage, Intracranial hemorrhage, Eye hemorrhage, Epistaxis, Gastrointestinal hemorrhage, Arterial hemorrhage, Bronchopulmonary hemorrhage, Bladder hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Tumor hemorrhage have been observed in AMG 386 (trebananib) trials.

[6]Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

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

Adverse events reported on AMG 386 (trebananib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AMG 386 (trebananib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (atrioventricular block second degree); Cardiac disorders - Other (intracardiac thrombus); Chest pain - cardiac; Heart failure; Mitral valve disease; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (inner ear fluid); Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Eye disorders - Other (blindness); Eye disorders - Other (central arterial occlusion); Eye disorders - Other (eye edema); Glaucoma; Papilledema; Uveitis; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Bloating; Colitis; Constipation; Dysphagia; Enterocolitis; Fecal incontinence; Flatulence; Gastric ulcer; Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal fistula; Gastrointestinal obstruction[6]; Gastrointestinal perforation[7]; Ileus; Mucositis oral; Pancreatitis; Rectal pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills[4]; Disease progression; Fever[4]; Flu like symptoms; Generalized edema; Localized edema; Malaise; Multi-organ failure; Non-cardiac chest pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (hepatitis toxic)
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (developed anti-trebananib binding antibodies)
INFECTIONS AND INFESTATIONS - Abdominal infection; Anorectal infection; Appendicitis; Infections and infestations - Other (nasopharyngitis); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection; Wound infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Spinal fracture; Wound complication; Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased[2]; GGT increased; INR increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (electrolyte imbalance)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Cerebrospinal fluid leakage; Dizziness[4]; Dysgeusia; Dysphasia[4]; Edema cerebral; Encephalopathy; Headache[4]; Hydrocephalus; Ischemia cerebrovascular; Muscle weakness left-sided; Nervous system disorders - Other (hemiplegia); Nervous system disorders - Other (left-sided hemineglect); Nervous system disorders - Other (loss of gag reflex); Paresthesia; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Insomnia; Mania; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury[2]; Hematuria; Urinary retention; Urinary tract obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Chylothorax; Cough; Dyspnea[4]; Hypoxia; Laryngopharyngeal dysesthesia; Pneumonitis; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disorder); Respiratory, thoracic and mediastinal disorders - Other (runny nose)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythroderma; Hyperhidrosis; Nail discoloration; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Rash acneiform; Rash maculo-papular[4]; Skin and subcutaneous tissue disorders - Other (abnormal hair growth); Skin ulceration
VASCULAR DISORDERS - Arterial thromboembolism; Flushing[4]; Hypotension[4]; Lymphedema; Peripheral ischemia; Vascular disorders - Other (vascular rupture)

Note: AMG 386 (Trebananib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Comprehensive Adverse Events and Potential Risks Lists (CAEPR for Commercial Agents

7.1.2.1 Bevacizumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Febrile neutropenia	
		Hemolytic uremic syndrome
CARDIAC DISORDERS		
	Cardiac disorders - Other (supraventricular arrhythmias)[2]	
		Chest pain - cardiac[3]
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction[3]
		Ventricular arrhythmia
		Ventricular fibrillation
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
	Constipation	
	Diarrhea	
	Dyspepsia	
		Gastrointestinal fistula[4]
	Gastrointestinal hemorrhage[5]	
	Gastrointestinal obstruction[6]	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Gastrointestinal perforation[7]
		Gastrointestinal ulcer[8]
	Ileus	
	Mucositis oral	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	
	Non-cardiac chest pain	
	Pain	
HEPATOBILIARY DISORDERS		
		Gallbladder perforation
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[9]	
		Infections and infestations - Other (necrotizing fascitis)
	Infections and infestations - Other (peri-rectal abscess)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]
	Wound complication	
	Wound dehiscence	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	Creatinine increased	
Neutrophil count decreased		
	Platelet count decreased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hypokalemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
		Avascular necrosis[11]
	Generalized muscle weakness	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]	
	Myalgia	
	Osteonecrosis of jaw[13]	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Intracranial hemorrhage
		Ischemia cerebrovascular
	Peripheral sensory neuropathy[14]	
		Reversible posterior leukoencephalopathy syndrome
	Syncope	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
	Hematuria	
		Nephrotic syndrome
	Proteinuria	
		Urinary fistula
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Reproductive system and breast disorders - Other (ovarian failure)[15]		
		Vaginal fistula
	Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	
		Bronchopleural fistula
		Bronchopulmonary hemorrhage
	Cough	
	Dyspnea	
	Epistaxis	
	Hoarseness	
		Pulmonary hypertension
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus	
	Rash maculo-papular	
	Urticaria	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
VASCULAR DISORDERS		
		Arterial thromboembolism[3,16]
Hypertension		
	Thromboembolic event	

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

[2]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal

stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

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

7.1.2.2 **Pazopanib**

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Pazopanib (Votrient, GW786034, NSC 737754)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for pazopanib (Votrient, GW786034).

Version 2.9, November 20, 2019[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Hemolytic uremic syndrome[2]
		Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS		
		Cardiac disorders - Other (Torsades de Pointes)
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction
	Sinus bradycardia	
ENDOCRINE DISORDERS		
	Hypothyroidism	
EYE DISORDERS		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Eye disorders - Other (eye hemorrhage, retinal hemorrhage)
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
Diarrhea		
	Dyspepsia	
		Gastrointestinal fistula[3]
		Gastrointestinal hemorrhage[4]
		Gastrointestinal perforation[5]
	Mucositis oral	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
INFECTIONS AND INFESTATIONS		
		Infection[6]
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	
Alanine aminotransferase increased		
	Alkaline phosphatase increased	
Aspartate aminotransferase increased		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Blood bilirubin increased		
	Creatinine increased	
		Ejection fraction decreased
		Electrocardiogram QT corrected interval prolonged
Lymphocyte count decreased		
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
	Hypercalcemia	
Hyperglycemia		
	Hyperkalemia	
	Hypermagnesemia	
	Hypernatremia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypoglycemia	
	Hypokalemia	
	Hypomagnesemia	
Hyponatremia		
	Hypophosphatemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Myalgia	
	Pain in extremity	

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Tumor pain	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
	Headache	
		Intracranial hemorrhage
		Reversible posterior leukoencephalopathy syndrome
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Hematuria
	Proteinuria	
		Urinary fistula
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
		Reproductive system and breast disorders - Other (female genital tract fistula)
		Uterine fistula
		Vaginal fistula
		Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Respiratory hemorrhage[7]	
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[8]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
Hair color changes		
	Palmar-plantar erythrodysesthesia syndrome	

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Rash maculo-papular	
	Skin hypopigmentation	
VASCULAR DISORDERS		
		Arterial thromboembolism[9]
Hypertension		
		Thromboembolic event[9]

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

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

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

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

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

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

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

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

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

Adverse events reported on pazopanib (GW786034) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pazopanib (GW786034) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Chest pain - cardiac;
Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood lactate dehydrogenase increased; Cardiac troponin T increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

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

7.1.2.3 **Sorafenib**

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Sorafenib (BAY 43-9006, NSC 724772)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2571 patients.* Below is the CAEPR for sorafenib (BAY 43-9006).

Version 2.10, June 24, 2020[1]

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
	Chest pain – cardiac	
		Heart failure
		Left ventricular systolic dysfunction

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Myocardial infarction
GASTROINTESTINAL DISORDERS		
Abdominal pain		
	Ascites	
	Constipation	
Diarrhea		
	Gastrointestinal hemorrhage[2]	
		Gastrointestinal perforation[3]
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Injury, poisoning and procedural complications - Other, specify (wound healing complication)
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	
Alanine aminotransferase increased		
Alkaline phosphatase increased		
Aspartate aminotransferase increased		
Blood bilirubin increased		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Creatinine increased		
		Electrocardiogram QT corrected interval prolonged
	GGT increased	
INR increased		
	Investigations - Other (Bicarbonate-serum low)	
Lipase increased		
Lymphocyte count decreased		
	Neutrophil count decreased	
Platelet count decreased		
Serum amylase increased		
		Thyroid stimulating hormone increased
Weight loss		
White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Hypercalcemia	
Hyperglycemia		
	Hyperkalemia	
	Hypernatremia	
Hypoalbuminemia		
Hypocalcemia		
	Hypoglycemia	
	Hypokalemia	
Hyponatremia		
Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 5.0 Term) [n= 2571]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Intracranial hemorrhage
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Respiratory hemorrhage[5]	
	Voice alteration	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
	Dry skin	
		Erythema multiforme
Palmar-plantar erythrodysesthesia syndrome		
	Pruritus	
Rash maculo-papular		
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
VASCULAR DISORDERS		
	Hypertension	
		Thromboembolic event

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be

distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

[4]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Respiratory hemorrhage may include bronchopulmonary hemorrhage, epistaxis, laryngeal hemorrhage, mediastinal hemorrhage, pharyngeal hemorrhage, and pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6]Febrile neutropenia is seen mostly in combination with other agents.

Adverse events reported on sorafenib (BAY 43-9006; Nexavar) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that sorafenib (BAY 43-9006, Nexavar) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy (e.g., TTP or HUS)); Febrile neutropenia[6]
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion, bilat); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual field distortion); Flashing lights; Keratitis; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fistula; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (small bowel NOS fistula); Gastrointestinal

fistula; Hemorrhoids; Ileal fistula; Ileus; Oral pain; Pancreatitis; Proctitis; Rectal fistula; Rectal mucositis; Rectal obstruction; Rectal pain; Small intestinal obstruction; Stomach pain; Visceral arterial ischemia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Facial pain; Flu like symptoms; Localized edema; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage; Hepatobiliary disorders - Other (biliary obstruction secondary to multiple biliary stones)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Cytokine release syndrome; Immune system disorders - Other (systemic inflammatory response syndrome)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Fall; Fracture; Hip fracture; Vascular access complication; Wound dehiscence

INVESTIGATIONS - CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; Fibrinogen decreased; Investigations - Other (blood urea nitrogen high)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hyperuricemia; Hypomagnesemia; Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (cramping); Myositis; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Muscle weakness left-sided; Muscle weakness right-sided; Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Libido decreased; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (focal segmental glomerulosclerosis); Renal and urinary disorders - Other (right ureter rupture); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urine discoloration

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Gynecomastia; Hematosalpinx; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal fistula; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchospasm; Hiccups; Hoarseness; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fibrosis; Respiratory, thoracic and mediastinal

disorders - Other (nasal septal perforation); Tracheal mucositis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Hyperhidrosis; Nail loss; Pain of skin; Purpura; Rash acneiform; Scalp pain; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratocanthomas type); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypotension; Phlebitis; Vascular disorders - Other (ruptured aortic aneurysm); Vasculitis

Note: Sorafenib (BAY 43-9006; Nexavar) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2.4 **Sunitinib**

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Sunitinib Malate (SU011248 L-malate, NSC 736511)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 7115 patients.* Below is the CAEPR for Sunitinib malate (SU011248 L-malate).
CTEP-AERS

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Hemolytic uremic syndrome
		Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS		
		Cardiac disorders - Other (cardiomyopathy)
		Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction
ENDOCRINE DISORDERS		
		Endocrine disorders - Other (thyroiditis)
		Hyperthyroidism
	Hypothyroidism	
EYE DISORDERS		
		Eye disorders - Other (macular edema)
	Papilledema	
		Vision decreased
GASTROINTESTINAL DISORDERS		
	Abdominal distension	
Abdominal pain		
Anal mucositis		
Constipation		
Diarrhea		
	Dry mouth	
Dyspepsia		
		Esophagitis

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Flatulence	
	Gastritis	
	Gastroesophageal reflux disease	
		Gastrointestinal perforation[2]
Mucositis oral		
Nausea		
	Oral pain	
		Pancreatitis
Rectal mucositis		
Small intestinal mucositis		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Flu like symptoms	
	Non-cardiac chest pain	
HEPATOBILIARY DISORDERS		
		Cholecystitis
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[3]
INFECTIONS AND INFESTATIONS		
		Infections and infestations - Other (necrotizing fasciitis)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Wound complication
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Creatinine increased	
		Electrocardiogram QT corrected interval prolonged
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypocalcemia	
		Hypoglycemia
	Hypophosphatemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
		Musculoskeletal and connective tissue disorder - Other (fistula formation)
	Myalgia	
		Osteonecrosis of jaw
	Pain in extremity	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy
		Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS		
	Dizziness	
Dysgeusia		
	Headache	
		Leukoencephalopathy
		Nervous system disorders - Other (cerebral infarction)
	Paresthesia	
		Reversible posterior leukoencephalopathy syndrome
		Transient ischemic attacks
PSYCHIATRIC DISORDERS		
	Depression	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Nephrotic syndrome
		Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
Laryngeal mucositis		
Pharyngeal mucositis		
Tracheal mucositis		

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
		Erythema multiforme
	Hair color changes	
Palmar-plantar erythrodysesthesia syndrome		
	Pruritus	
	Rash maculo-papular	
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)
	Skin hypopigmentation	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
VASCULAR DISORDERS		
	Hypertension	
		Thromboembolic event
	Vascular disorders - Other (hemorrhage)[4]	

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

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

[3]Allergic reactions observed include anaphylaxis and angioedema.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal

intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported.

Adverse events reported on Sunitinib malate (SU011248 L-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Sunitinib malate (SU011248 L-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion
GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain
INVESTIGATIONS - GGT increased; INR increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Peripheral sensory neuropathy; Seizure; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Hematuria; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax
VASCULAR DISORDERS - Flushing; Hypotension

Note: Sunitinib malate (SU011248 L-malate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.

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

7.3. Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.
Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** under the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

7.4. Routine Adverse Event Reporting

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

7.5. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

7.6. Second Malignancy

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

7.7. Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "pregnancy, puerperium and perinatal conditions - Other (Pregnancy)" under the Pregnancy, puerperium and perinatal conditions SOC and reported as Grade 3.

When submitting the CTEP-AERS report for pregnancy, the "Pregnancy Information Form" should be completed and faxed along with any additional medical information to (301) 230-0159 (see Appendix D). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the Description of Event section of the CTEP-AERS report.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physician(s). The "Pregnancy Information Form" should be used for all follow-ups. If the baby is born with a birth defect or other anomaly, then a second CTEP-AERS report is required.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1. AMG 386 (NSC 751173)

Chemical Name: N/A

Other Name: -trebananib

Classification: Anti-angiopoietin peptibody

M.W.: 63.5 kD

Approximate Solubility: N/A

Mode of Action: AMG 386 selectively inhibits angiopoietins, thereby blocking the interaction between Ang1 and Ang2 with their receptor Tie-2. By inhibiting Ang1 and Ang2 from binding to Tie2 receptors, AMG 386 results in an anti-tumor effect. In nonclinical studies, AMG 386 reduced proliferation of tumor endothelial cells and inhibited the growth of human xenograft tumors in mice, while having minimal effects on normal tissues.

Description: A non-glycosylated homodimer consisting of IgG1 Fc domain with 4 copies of an anti-Ang2 peptide. Each monomeric unit contains 10 cysteine residues that are involved in 4 intrachain disulfide bonds and 2 interchain disulfide bonds. AMG 386 contains 287 amino acids.

How Supplied: Amgen, Inc., supplies and CTEP/DCTD distributes AMG 386 as a 150 mg, 240 mg, and 600 mg lyophilized powder for Injection vials packaged in 20 mL, 20 mL, and 50 mL vial sizes, respectively. AMG 386 is a single-use vial, sterile, preservative-free, and contains 10 mM histidine, 4% (w/v) mannitol, 2% (w/v) sucrose, 10 mM arginine hydrochloride, and 0.01% (w/v) polysorbate 20 to a pH of 7.1.

Currently, the 240 mg vials are being used in all CTEP sponsored protocols. Once the NCI has depleted the 240 mg supply, stop using the dosing tables that are currently available in the protocol. All calculated dose in Dose Levels 10mg/kg, 15 mg/kg, and 30 mg/kg will be rounded to the nearest vial size using 150 mg or/and 600 mg vials. Please refer to Appendix H for dose rounding guidelines that use the 150 mg and 600 mg vials.

AMG 386 (mg) per vial	Volume SWFI for reconstitution (mL)
150	5
240	8

600	20

Preparation: Take the vial(s) out of the refrigerator only when ready to prepare the drug for patients.

Note: Amgen Inc. does not classified AMG 386 as cytotoxic; however, if and only if your site requires the use of vial adaptors, a 0.2 µm PES (polyethersulfone) in-line filter must be used during the IV administration to reduce the risk of stopper particles in the IV solution.

Step 1: Make 30 mg/mL stock solution:

1. Reconstitute vial within 3 hours once removed from the refrigerator. If it is not reconstituted within 3 hours, discard the drug.
2. Inject the required volume of sterile Water for Injection as indicated in the table above into the drug vial with the needle directed toward the side of the vial to avoid foaming. This results in a 30 mg/mL solution. Do not use bacteriostatic water.
3. Swirl gently until all lyophilized powder is dissolved. Dissolution usually takes 2 minutes or less. The diluted solution is clear, colorless to slightly yellow.
4. Do not shake.
5. This stock solution is stable up to 1 hour when stored at ambient temperature and up to 24 hours when refrigerated at 2^0 to 8^0C, protected from light.

Step 2: Reconstitute the final IV product:
Withdraw the calculated amount of the drug from the stock solution (30 mg/mL) and further dilute it in 0.9% Sodium Chloride Injection, USP to a final concentration between **1.2 mg/mL – 30 mg/mL**. The prepared IV bag can be stored at ambient temperature, protected from light for up to 6 hours (i.e., from the time the drug is diluted in 0.9% NS to the time it is ready to be administered). The final IV bag must be protected from light if not used immediately.

Storage: Refrigerate the intact vials at 2˚ to 8˚ C upon receipt. Protect the vials from light. Do not freeze.

The prepared IV bag can be stored at ambient temperature, protected from light for up to 6 hours (this does not include the 1 hour preparation of the stock solution) before administration.

Stability: Shelf-life studies of AMG 386 are ongoing. The stock solution (30 mg/mL) is stable up to 1 hour at ambient temperature and up to 24 hours refrigerated at 2˚ to 8˚ C, protected from light. The final IV solution is stable up to 6 hours at ambient temperature, and **must be protected from light if not used immediately**..

Route(s) of Administration: Intravenous.

Method of Administration: Infuse over 60 minutes via an infusion pump. If well tolerated, subsequent infusions can be given over 30 minutes. Flush the IV line with 0.9% NS (minimum volume is 5 mL) before and after the each IV infusion.
Note: the IV bag does not need to be protected from light during the IV infusion).

Potential Drug Interactions: Coadministration of VEGF inhibitors (motesanib, sorafenib, sunitinib, and bevacizumab) and/or chemotherapeutic agents (FOLFOX, FOLFIRI, paclitaxel, docetaxel, carboplatin, cisplatin, PLD, topotecan, and capecitabine) has not been demonstrated to alter the pharmacokinetics (Cmax or AUC) of AMG 386.

Patient Care Implications: If extravasation occurs follow your institutional guidelines for treatment. Mild to moderate edema, usually in the upper and/or lower extremities, has occurred when AMG 386 is given concomitantly with other drugs. Co-administration of AMG 386 with sorafenib may result in retinal artery thrombosis, which can result in permanent impairment of vision or vision loss.

Availability

AMG 386 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. AMG 386 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.1 Agent Ordering and Agent Accountability

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

Submit all agent requests electronically to PMB. Active CTEP-registered investigators and investigator-designated shipping designees

and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.1.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2. Commercial Agents

8.2.1 Bevacizumab (Avastin®)

Product description: Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Bevacizumab is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

Bevacizumab (Avastin®) is commercially available.

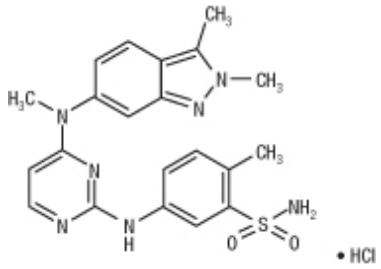
Solution preparation: Please refer to the package insert for preparation instructions.

Route of administration: Administer bevacizumab only as an intravenous (IV) infusion. Do not administer as an intravenous push or bolus.
• First infusion: Administer infusion over 90 minutes.

• Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

8.2.2 **Pazopanib (Votrient™)**

Product description: Pazopanib is a tyrosine kinase inhibitor (TKI). Pazopanib is presented as the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. It has the molecular formula C21H23N7O2S•HCl and a molecular weight of 473.99. Pazopanib hydrochloride has the following chemical structure:



Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

Each 200 mg tablet of pazopanib contains 216.7 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base.

The inactive ingredients of pazopanib are: Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. Coating: Gray film-coat: Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, titanium dioxide.

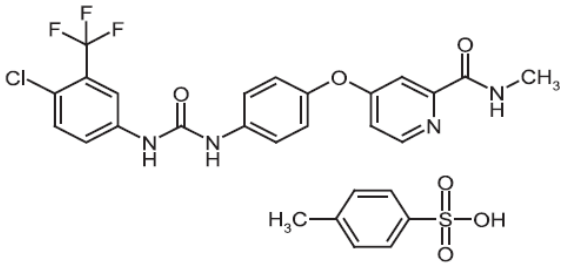
Pazopanib (Votrient™) is commercially available.

Route of administration: Pazopanib tablets are for oral administration.

Please consult the package insert for the drug administration guidelines and other clinical information.

8.2.3 **Sorafenib (Nexavar®)**

Product description: Nexavar®, a kinase inhibitor, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-(3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido)phenoxy)N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of C21H16ClF3N4O3 x C7H8O3S and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Each red, round Nexavar® film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

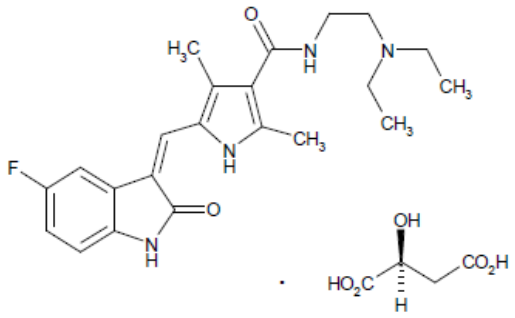
Sorafenib (Nexavar®) is commercially available.

Route of administration: Sorafenib tablets are for oral administration.

Please consult the package insert for the drug administration guidelines and other clinical information.

8.2.4 Sunitinib (Sutent®)

Product description: Sunitinib (Sutent®), an oral multi-kinase inhibitor, is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is C22H27FN4O2 x C4H6O5 and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

Sunitinib malate capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. The white printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

Sunitinib (Sutent®) is commercially available.

Route of administration: Sunitinib capsules are for oral administration.

Please consult the package insert for the drug administration guidelines and other clinical information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Tumor Tissue-Based Correlative Studies

9.1.1 Pre-Treatment Biopsy

Assent to performing a fresh tumor biopsy is a requirement of this trial. Refer to Section 5.1 for details regarding the timing and performance of this biopsy. Paraffin blocks will be made and processed according to standard institutional protocols. Paraffin-embedded tissue blocks containing formalin-fixed tumor must be submitted for evaluation of expression of relevant molecular targets.

9.1.2 Archival Specimen

Submission of an archival tumor specimen is a requirement for participation on this trial. An unstained tumor block from the original resection is preferred. Where an archival block cannot be released by the governing pathology department, 5 x 6μm re-cuts on 10-12 slides is requested.

9.1.3 Specimen Handling and Shipping

Biopsy specimens will be collected in formalin and embedded in paraffin by the local pathology department. See Appendix F for shipping instructions.

9.1.4 Methodology

Gene expression profiling will be performed in a CLIA-certified laboratory (Response Genetics Inc.). Each block will be reviewed for quality and tumor content by a board-certified pathologist. Ten μm-thick sections will be prepared from identified areas with the highest tumor concentration. Manual micro-dissection using a light microscope will be performed on all tumor samples to ensure >80% tumor cells is dissected. RNA isolation from paraffin-embedded samples will be performed according to a proprietary procedure defined by Response Genetics. After RNA isolation, cDNA will be prepared from each sample. Quantitation of the genes of interest and an internal reference (β-actin) cDNA will be performed using a fluorescence-based real-time detection method (ABI PRISM 7900HT Sequence detection System [TaqMan®] Applied Biosystems, Foster City, CA). The polymerase chain reaction mixture consists of primer, probe, AmpliTaq Gold Polymerase, the dNTP mixture and the TaqMan Buffer. A reference dye is added to a final reaction volume which is 20 μL (all reagents from Applied Biosystems, Foster City, CA).

All samples will be amplified in triplicate for each gene. For each sample, parallel TaqMan polymerase chain reactions will be performed for the gene of interest and the β-actin reference gene to normalize the gene expression. The obtained ratio between the values provides relative gene expression levels for each gene of interest. Markers

will be prioritized in the following order in the absence of sufficient tissue to perform all of the markers on a given specimen:

Markers of angiopoietin-Tie2 mediated angiogenesis

- Ang1
- Ang2
- Tie2

Markers of VEGF-pathway mediated angiogenesis

- VEGF
- VEGFR1
- VEGFR2
- NRP-1

Markers of alternative pro-angiogenic pathways

- IL-8
- VCAM-1
- bFGF

9.2. Pharmacodynamic Correlative Studies

9.2.1 Plasma Collection

One purple top blood tube (EDTA), ~10 mL, will be collected at baseline (prior to cycle 1), prior to cycle 2, prior to cycle 3, and at progression. It is important that blood is collected at all timepoints and that the specimens are consistently processed according to protocol instructions.

9.2.2 Specimen Handling and Shipping

The EDTA tube should be spun in a standard laboratory centrifuge to separate plasma, buffy coat cells, and red blood cells (**see Appendix F for blood handling protocol**). All tubes should be frozen as rapidly as possible, and then stored in a -70° C freezer until shipped. See Appendix F for shipping instructions.

9.2.3 Methodology

Biomarker levels will be multiplexed where possible using multiplex bead suspension arrays and analyzed using the Luminex xMAP® system (Luminex Corporation, Austin, Tx). Individual Enzyme-linked Immunosorbent Assays (ELISAs) will be performed for the remaining markers and where Fc depletion is required. Analyses will be performed by the laboratory of Dr. Philip Mack. The following markers will be measured (listed in order of priority if sample is insufficient to perform all markers):

Markers angiopoietin-Tie2 pathway activity

- Ang2
- soluble Tie2

Markers of VEGF pathway activity

- VEGF-A
- soluble VEGFR2

Markers of alternative pro-angiogenic pathways

- IL-8
- ICAM-1
- VCAM-1
- bFGF
- PDGF
- PlGF

9.3. Pharmacogenetic Correlative Studies

9.3.1 Specimen Collection

Genomic DNA will be collected from peripheral blood mononuclear cells will be collected at baseline (prior to cycle 1).

9.3.2 Specimen Handling and Shipping

A separate sample is not required for pharmacogenetic analysis. White blood cells containing genomic DNA will be isolated from the buffy coat layer as described in section 9.2.2.

9.3.3 Methodology

Polymorphisms in these genes will be analyzed by polymerase chain reaction-restriction length polymorphism (PCR-RFLP) as previously described (Schneider et al. 2008). Pharmacogenetic analysis will be performed in the laboratory of Dr. Heinz Lenz. Polymorphisms in the following genes will be analyzed:

VEGF- pathway

- VEGF-A
- VEGFR2
- PlGF

Angiopoietin-Tie2 pathway

- Ang1
- Ang2
- Tie2

Alternative pro-angiogenic pathways

- IL-8
- ICAM-1
- VCAM-1
- FGFR4

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 72 hours prior to initiation of the next cycle of therapy. Cycle length is defined as 6 weeks. Unless otherwise specified, assessments may be performed within a 72 hour window of the indicated timepoint.

	Pre-Study	Wk -1	Wk 1[j]	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13+	Off Study[k]
AMG386			A	A	A	A	A	A	A	A	A	A	A	A	A	
Bevacizumab			B		B		B		B		B		B		B	
Pazopanib			C	C	C	C	C	C	C	C	C	C	C	C	C	
Sorafenib			D	D	D	D	D	D	D	D	D	D	D	D	D	
Sunitinib			E	E	E	E			E	E	E	E			E	
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X		X----------X													
Physical exam	X		X	X		X			X			X			X	X
Vital signs (including BP)	X		X	X		X			X			X			X	X
Height	X															
Weight	X		X	X		X			X			X			X	X
Performance status	X		X	X		X			X			X			X	X
CBC w/diff, plts[a]	X		X	X		X			X			X			X	X
Serum chemistry[a,b]	X		X	X		X			X			X			X	X
Serum Liver Tests (for patients on Pazopanib only)[l]			X		X		X		X		X			X		
Coagulation[c]	X															
TSH, free T4[d]	X														X	
Urine dipstick	X								X						X	
EKG (as indicated)	X								X						X	
Echo/MUGA (as indicated)[f]	X															
Adverse event evaluation			X----------X													X
Tumor measurements	X		Tumor measurements are repeated every 12 weeks (+/- 7 days). Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X
Radiologic evaluation	X		Radiologic measurements should be performed every 12 weeks (+/- 7 days).													X
B-HCG	X[g]															
Research Tumor Biopsy[h]		X														
Archival Tumor Specimen	X															

Correlative Collection[i]			X						X						X	X

A: AMG386: 15 mg/kg IV weekly (D1, 8, 15, 22, 29, and 36)
B: Bevacizumab: 10 mg/kg IV every 2 weeks (D1, 15, and 29)
C: Pazopanib: Dose as assigned. Once daily orally.
D: Sorafenib: Dose as assigned. Twice daily orally.
E: Sunitinib: Dose as assigned. Once daily for 4 weeks, followed by 2 week rest period.
a: Laboratory tests will be done within 14 days prior to registration. Laboratory tests will also be repeated within 72 hours of treatment on week 1, week 2, week 4 and then every 3 weeks (twice per cycle)
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c: Prothrombin time / INR, activated partial thromboplastin time
d: TSH, free T4 performed once every other cycle. Required only for patients on pazopanib, sunitinib, or sorafenib.
e: Urine dipstick will be performed at baseline once per cycle. See section 6.6.
f: LVEF assessment ≤4 weeks prior to registration: required for patients with history or symptoms of congestive heart failure.
g: Serum pregnancy test (women of childbearing potential).
h: To be performed within 1 week after registration. See Section 5.1.
i: Blood for correlatives will be collected at baseline, prior to cycle 2, prior to cycle 3, and at progression.
j: Treatment should begin between 3 and 5 working days after completion of tumor biopsy and after complete recovery from the biopsy procedure.
k: Off-study evaluation.
1: Serum liver tests should be monitored before initiation of treatment with pazopanib and at weeks 3, 5, 7, and 9. Thereafter, monitoring should occur at months 3 and 4, and as clinically indicated. Periodic monitoring should continue after month 4.

11. MEASUREMENT OF EFFECT

11.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

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

11.2. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AMG 386.

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

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

11.2.1 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT

scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.2.2 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the

positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.3. Response Criteria

11.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for

PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.3.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

11.3.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	≥4 wks. Confirmation**
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.4. Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

11.5. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1. Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be

submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

Either the Coordinating Center or the Lead Organization is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.1.3. Data Collection Forms and Submission Schedule

All data will be collected using COH data collection forms via an electronic data capture system. Any original data collection forms will reside at the originating institutions in secure location.

ELIGIBILITY CHECKLIST: The data manager at the registering site will have completed and faxed this form at the time of registration.
ON-STUDY FORM (FORM OS): Completed on-study forms due within two weeks of registration.
TREATMENT FORM (FORM RX): Completed treatment forms are due within four weeks of completion of a cycle.
ADVERSE EVENT COLLECTION: Completed adverse events collection form due within four weeks of completion of a cycle.
FLOW SHEETS: Protocol specific flow sheets are to be submitted along with each treatment form.
RESPONSE/OFF-STUDY/FOLLOW-UP: Form F/U is to be submitted each time a patient is evaluated for response and/or new follow-up information is

obtained.
SUPPLEMENTAL DATA FORM: The timeline for submission of the supplemental data form will be protocol specific, if applicable.

12.2. CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.3. Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

Party Data"):

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to

Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

Design: This is a randomized phase II study in patients with advanced renal cell carcinoma. Patients will be randomized to treatment with AMG 386 monotherapy (arm A) or AMG 386 plus bevacizumab, pazopanib, sorafenib, or sunitinib (arm B). This phase II trial is designed to assess efficacy of each arm.

Primary Endpoint: The primary endpoint of this trial is treatment efficacy evaluated by overall tumor response rate (ORR) using RECIST v1.1 criteria in each treatment arm. The overall tumor response rate is defined as the total number of efficacy-evaluable patients who achieve a complete or partial response by RECIST 1.1 criteria.

In this study we will define as **efficacy-evaluable**, any eligible patient who began therapy (and received any amount of the first dose of AMG 386).

13.2. Sample Size/Accrual Rate

For assessment of clinical outcome, both arms will be evaluated separately using a Simon Optimum design with as maximum of 39 patients, an interim evaluation after 17 patients, and with alpha=0.10 (when the response rate is $\leq$ 3%) and beta=0.10 (when the response rate is 15%). If AMG 386 is ineffective (alone or in the presence of an anti-VEGF agent), then we would expect to see no objective responses (by RECIST v1.1), while a 15% response rate would be taken as interesting enough to encourage future study. Thus, if 0/17 or $\leq$ 2/39 patients experience an objective response within each arm, this will be taken as evidence that the response rate in that arm is less than 15%. Conversely, if 3 or more patients out of 39 experience an objective response, that will be taken as evidence that the true response rate is greater than 3%. Based on prior accrual, the accrual rate is anticipated to be 4 patients per month.

13.3. Analysis of Secondary Endpoints

Secondary Endpoints:
1) To evaluate progression free survival in each arm.
2) To evaluate the tolerance and toxicity of AMG 386 alone and in combination with continuation of the prior VEGF targeted regimen.

Progression free survival (PFS): Progression free survival, defined as the duration of time from start of treatment to time of progression or death, whichever occurs first, will be analyzed in the efficacy-evaluable population.

Monitoring Safety/Toxicity: Safety and toxicity will be reviewed monthly at the CCCP Data Coordinating Meetings, in which all toxicities (especially Grade 3+) are assembled and reviewed. The first 6 patients treated with the combination of each anti-VEGF agent and AMG 386 will be specifically monitored during these calls. In addition, safety boundaries (using a modified sequential probability ratio test) will be used to flag excessive, unacceptable toxicities. Additionally, because there is limited experience with AMG 386 at 15 mg/kg in combination with anti-VEGF agents and due to a mandate for tumor biopsy in the RCC cohort, there will be separate dedicated monthly conference calls for this trial monitoring toxicity events and the safety of the mandatory research biopsy.

Rules for Monitoring Safety: In this trial, unacceptable toxicity (TOX) will be defined as any toxicity due to treatment, that results in a death. Patients who complete the first course of treatment (i.e. receive 80% of the total planned amount of AMG 386 (accounting for dose reductions as specified in the protocol), or who fail to complete the first course for reasons of toxicity or side effects, will be considered at risk for TOX (for purposes of applying these toxicity monitoring boundaries).

Criteria for flagging an excessive number of patients with TOX are based on the sequential probability ratio test with α=0.10, β=0.05, p_o=0.03 and p_a=0.15. Every time a patient is classified as having had a TOX, the cumulative number of patients (X) who have experienced a TOX will be compared to the number of patients (N) who are at risk. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then the boundary has not been crossed. If N is less than or equal to N_X, then the boundary has been crossed and a careful review of all the toxicities and tolerability will be initiated.

Table: Boundary for Monitoring Toxicity				
X: # pts who experienced a TOX	2	3	4	5
N_x: Boundary crossed if # pts. At risk (N) is ≤ N_x	≤9	≤22	≤35	≤39

These rules were selected to ensure a reasonable chance that the boundary would not be crossed if the true chance of TOX were less than 3-5% and a reasonable chance that the boundary would be crossed if the true chance were 15-20%. The Table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Table: Probability that the Toxicity Monitoring Boundary is Crossed Because Too Many Patients Experienced a TOX						
True Chance of an Unacceptable Toxicity (TOX)		**3%**	**5%**	**10%**	**15%**	**20%**
Probability of Suspending Accrual to Review Toxicities	N=17	0.03	0.10	0.32	0.56	0.74
	N=39	0.05	0.17	0.56	0.85	0.96

Summary of Clinical Endpoints: All patients who begin treatment with AMG 386 will be accounted for, in each of the 2 arms separately; number of prior chemotherapy regimens, prior treatment with an mTOR inhibitor, number of courses begun, number of courses completed, reason off treatment, reason off study, total drug(s) received, toxicities (grade, type, cycle, and attribution) experienced, best response, and time to progression will be listed for each patient and summarized using standard descriptive methods – point estimates and associated confidence intervals. Kaplan-Meier plots will be used to display the PFS in each arm.

13.4. Analysis of Correlative Endpoints

Correlative Endpoints:
1) To evaluate the association between pretreatment tumor gene expression levels and response to AMG 386 in combination with continuation of the prior VEGF targeted agent.
2) To evaluate the association between SNPs in angiogenic genes and response to AMG 386 in combination with continuation of the prior VEGF targeted agent.
3) To compare changes in circulating angiogenic factors in RCC patients treated with AMG 386 monotherapy to those treated with AMG 386 in combination with VEGF-targeted therapy.
4) To compare expression of angiogenic genes in RCC tumors from archival specimens to the expression in biopsy specimens performed after progression on anti-VEGF therapy.

The long-range goal should AMG 386, alone or with VEGF-targeted therapy, prove to be effective in the treatment of RCC, would be to identify subsets of patients who are more likely (or who are very unlikely) to benefit from treatment with AMG 386 – using baseline archival or biopsy tumor specimens. The first step in identifying predictive markers is simply to establish an association with outcome. Follow-up studies will be needed, to better quantify the relationships and to accurately estimate the sensitivity and specificity of individual markers, or a panel of markers, for predicting response to AMG 386.

The analyses and descriptions below assume that we will be using objective response (CR+PR vs. SD+PD) as the clinical outcome variable to evaluate the potential predictive biomarkers. However, in addition, we will repeat the analyses using (1) progression-free-survival (PFS) (with Kaplan-Meier plots, the logrank test and the Cox proportional hazards model, instead of scatterplots, t-tests, contingency tables

and associated chi-square tests and logistic regression) and (2) using the percent change in tumor burden by RECIST v1.1 (with scatterplots, correlations, and linear regressions) to assess whether biomarker patterns have the potential for identifying patients who are more or less likely to benefit from treatment with AMG 386. These additional analyses will serve two purposes: (1) if there are strong patterns, we would expect to observe them using other metrics of anti-tumor activity, and (2) in an exploratory fashion, they may reveal patterns that are not apparent with the dichotomous response rate.

The levels of the circulating angiogenic factors will be analyzed as continuous variables (most likely after transformation). The gene expression results from the pretreatment tumor biopsies are expressed as ratios between that of the gene of interest and the internal reference gene β-actin and can be analyzed as continuous variables – generally after log transformation. Polymorphisms are categorical; generally the wildtype homozygous genotype is compared to the genotypes containing the less frequent allele.

The initial analysis of tumor gene expression will be performed on pre-treatment tumor biopsies. At a minimum, there will be study specimens for 17 patients who receive AMG 386 alone and 17 patients who receive AMG 386 with an anti-VEGF agent; if AMG 386 demonstrates anti-tumor activity in RCC, then we will have specimens for 39 patients in arm A and arm B respectively.

(1) The expression of angiopoietin-, VEGF-, and anti-angiogenic therapy resistance-related markers will be compared between archival specimens and the research biopsy specimens. Both archival and biopsy specimens will be sought for all patients. Assuming specimens are available for 90% of patients, we anticipate that there will be 30 (90% of 17+17) or 50 (90% of 17+39) or 70 (90% of 39+39) paired specimens allowing the comparison of the gene expression levels in archival specimens (before anti-VEGF therapy) with levels in biopsy specimens (after anti-VEGF therapy). In addition to comparing the mean levels and patient-to-patient variability based on the two sets of specimens, we will be especially interested in whether the two types of specimens result in the same ranking of patients according to each of the gene expression levels; thus, the Spearman correlation coefficient, and associated 95% confidence interval will be calculated. The table below provides the 95% confidence intervals for a selection of possible observed correlation coefficients. The observed correlation coefficients will be used to better understand whether the archival specimens convey the same information as the biopsy specimens.

Table: Example of 95% Confidence Intervals for Possible Observed Spearman Correlation between Gene Expression Levels Determined in Archival Specimens and Determined in Biopsy Specimens

Observed Correlation	95% Confidence Interval with 30 Pairs of Specimens (90% of 17+17)	95% Confidence Interval with 50 Pairs of Specimens (90% of 17+39)
0.60	(0.31, 0.79)	(0.39, 0.75)
0.65	(0.38, 0.82)	(0.45, 0.79)
0.70	(0.46, 0.85)	(0.52, 0.82)

0.75	(0.54, 0.87)	(0.60, 0.85)
0.80	(0.62, 0.90)	(0.67, 0.88)
0.85	(0.71, 0.93)	(0.75, 0.91)
0.90	(0.80, 0.95)	(0.83, 0.94)

(2) ***The observed clinical activity of AMG 386 (+/- anti-VEGF therapy) will determine how the biomarker data will be examined and used.*** To illustrate this, two possible scenarios are described: (a) If AMG 386 +/- anti-VEGF therapy is inactive and no responders are observed in any of the 2x17=34 patients, and (b) the drug combination AMG 386 (+ anti-VEGF therapy) has demonstrated activity and there are at least 3 patients with objective responses in 39 patients (if 15% of patients have an objective response, we can expect about 5-6 responders).

(a) If AMG 386 + anti-VEGF therapy demonstrates no (or very little) activity, tumor gene expression levels, the polymorphisms and the baseline circulating angiogenic factors will be summarized – overall and by disease. The changes, at the 2nd and 3rd cycles, in the circulating levels will also be summarized (using standard descriptive statistics); t-tests for each marker (and possibly the multivariate Hotelling's T2) will be used to evaluate whether there were any changes at all (overall) and whether the changes were in the hypothesized favorable direction – if necessary, adjusting for disease. These patterns – baseline and changes, or lack of changes – may help to explain why AMG 386 + anti-VEGF therapy was inactive. That is, these analyses can be used to understand whether the expected biological (PD) effects were observed and thus this trial will provide important information even in the absence of clinical activity. In this setting, the use of PFS or percent change in tumor burden may reveal signals or patterns that are not apparent with the dichotomous response rate.

(b) If AMG 386 + anti-VEGF therapy is shown to be active, then scatterplots, means, and confidence intervals will be used to display the differences between the responders and non-responders, in terms of each of the continuous biomarkers – at baseline and the changes. The two groups will be compared in terms of polymorphisms, using methods for categorical data. Of particular interest is the possibility that this agent is reasonably effective in a subset of patients and essentially ineffective in the remaining patients – and that this subset can be defined by one correctly identified biomarker. These proposed descriptive analyses will identify very strong patterns should they exist (e.g. if there are 4 or 5 responders and all 4 or 5 have expression levels for a marker that are all above or all below the median). The purpose of these exploratory analyses is to revise and refine hypotheses regarding the role of AMG 386 in the treatment of RCC – with the understanding that these new hypotheses will require testing.

No formal adjustment will be made to account for the number of comparisons; if warranted, resampling will be used to assess the robustness (internal validity) of the identified differences and patterns. The goal of these analyses – in addition to better understanding why tumors did or did not respond – is to identify a subset of biomarkers which can be further studied should this agent undergo additional testing.

13.5. Reporting and Exclusions

13.5.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with AMG 386, bevacizumab, pazopanib, sorafenib, or sunitinib.

13.5.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

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

14. CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase II trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7) and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCCP teleconference meeting for review and approval.

Oversight
Oversight of the conduct of CCCP trials occurs at several levels:

1. The Data Coordinating Center for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. CTEP specifics the monitoring method for NCI-sponsored protocols coordinated by the CCCP. For trials monitored by the NCI-designated clinical trials monitoring service (CTMS), CTMS will audit patients' records on each protocol – at each participating institution; these audits are initiated by CTEP. For all other CCCP trials, patient records at each institution are audited in accord with institutional cancer center policies.

3. An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 5 voting members (3 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCCP studies, a statistician, and a patient advocate) and a non-voting CCCP statistician.

    a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
    b. This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.

c. The DSMC will report to the CCCP leadership.

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APPENDIX A - Performance Status Criteria

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

APPENDIX B - CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C - List of drugs that may have potential CYP3A4 interactions

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Delavirdine	Isosorbide	Primaquine	Zonisamide
Diazepam	Isosorbide dinitrate	Progesterone	Zopiclone
	Isosorbide mononitrate	Quetiapine	

CYP3A4 Inhibitors

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

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (2)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

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

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

(1) Malhotra *et al*. (2001). Clin Pharmacol Ther. 69:14-23.

(2) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249.
Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329.

Updated on May 1, 2007

APPENDIX D – Pregnancy Information Form

The following form must be submitted as described in Section 7.7.

Attach to AdEERS Report

PREGNANCY INFORMATION FAX

FACSIMILE TRANSMISSION

Ticket Number:_____

Study #:

SAF FAX NO: (301) 230-0159

ALTERNATE FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD - MMM - YY)	Follow-up Report Date: ___ - ___ - ___ (DD - MMM - YY)
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number | Subject Number

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male

Subject's Weight: _____ kg

Subject's Date of Birth: ___ - ___ - ___ (DD - MMM - YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug:	Study Drug Start Date: ___ - ___ - ___ (DD - MMM - YY) Study Drug Stop Date: ___ - ___ - ___ (DD - MMM - YY) OR ☐ Study Drug Continuing		
Dose:	Route: **ORAL**	Frequency: **QD**	Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD - MMM - YY) Estimated Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Method of Contraception (check all that apply):

☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide

☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown

☐ CVS Results: ☐ Normal ☐ Abnormal ☐ Amniocentesis Results: ☐ Normal ☐ Abnormal ☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome

Was pregnancy interrupted? ☐ Yes ☐ No

If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic

Date of Termination: ___ - ___ - ___ (DD - MMM - YY)

If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)

☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

NOTE: For an initial reporting fax both the Pregnancy Report CRF and Additional Pregnancy Information Fax Page. For follow-up reporting, fax only the Additional Pregnancy Information Fax Page.

FAXP_CS 1 8/14/08 1.0

APPENDIX E – Pill Diaries

Today's date _____ **Agent: Pazopanib**

Patient Name _____ (*initials acceptable)* **Patient Study ID** _____

Instructions to Patients: You will receive **pazopanib in 200mg** tablets. Your doctor will tell you how many tablets to take each day. Pazopanib should be ingested with a glass of water at least 1 hour before food or at least 2 hours a meal. You should try and take your daily dose of dovitinib at approximately the same time each day. Do not crush pazopanib tablets.

Day	Date	Time of Dose	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				

Patient's signature

Physician's Office will complete this section:

1. Patient's planned total daily dose _____
2. Total number of tablets taken this month _____
3. Physician/Nurse/Data Manager's Signature _____

Today's date _____ **Agent: Sorafenib**

Patient Name _____ (*initials acceptable)* **Patient Study ID** _____

Instructions to Patients: You will receive **sorafenib in 200mg** tablets. Your doctor will tell you how many tablets to take each day. You will take sorafenib twice each day. Sorafenib should be ingested with a glass of water at least 1 hour before food or at least 2 hours a meal.

Day	Date	Time of Dose	# of tablets taken AM	# of tablets taken PM	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					
35					
36					
37					
38					
39					
40					
41					
42					

Patient's signature

Physician's Office will complete this section:
1. Patient's planned total daily dose _____
2. Total number of tablets taken this month _____
3. Physician/Nurse/Data Manager's Signature _____

Today's date _____ **Agent: Sunitinib**

Patient Name (*initials acceptable)* **Patient Study ID**

Instructions to Patients: You will receive **sunitinib in** 50 mg, 25 mg, or 12.5 mg tablets. Your doctor will tell you how many tablets to take each day. Sunitinib can be taken with or without food. You should try and take your daily dose of sunitinib at approximately the same time each day.

Day	Date	Time of Dose	# of tablets taken			Comments
			50mg	25mg	12.5mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29	**Do Not Take Sunitinib Days 29-42.**					
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						

Patient's signature

Physician's Office will complete this section:
1. Patient's planned total daily dose _____
2. Total number of tablets taken this month _____
3. Physician/Nurse/Data Manager's Signature _____

APPENDIX F - Specimen Shipment Guidelines

1. **Tumor Biopsy Specimens**

Archived and protocol specific biopsy specimens will be collected in formalin and processed by the local pathology department. Processed specimens will then be submitted to the laboratory of Dr. Philip Mack. Institutions should notify the recipient by either phone or fax prior to shipping specimens. This will allow the recipient to track the package in the event that there are any problems in delivery. All archival paraffin block/slide specimens should be sent at ambient temperature. Specimens should be shipped to the following address:

Philip C. Mack, PhD
UC Davis Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817
Laboratory Phone: 916-734-3734
Fax: 916-734-2361
Email: philip.mack@ucdmc.ucdavis.edu

2. **Blood Specimens**

Cryovials (1.5 – 2 mL size) must be labeled with the protocol number (PhII-122), Consortium patient ID, patient's initials, date of specimen collection, and specimen type.

- Collect ~10 mL whole blood in a purple top (EDTA) tube.
- Immediately invert tube (gently) 8 – 10 times. This reduces the possibility of clot formation.
- Place tube on wet ice or refrigerate until centrifugation.
- Within 2 hours of blood draw, centrifuge sample at 800 x G for 10 minutes.
- Immediately after centrifuging, transfer plasma to a new, sterile 15 mL conical centrifuge tube.
    - Pipette slowly to avoid disturbing the buffy coat layer.
    - Leave a small amount of plasma (~ .5 cm) above the buffy coat layer.
    - Centrifuge plasma at 1500 x G for 10 minutes to pellet any remaining platelets. After the second spin, transfer the plasma in 1 mL aliquots to 4 labeled cryovials, taking care to avoid the pellet at the bottom of the tube.
- While plasma is being centrifuged for the second time, transfer buffy coat from the original EDTA tube to 1 labeled cryovial.
    - The buffy layer is the off-white layer between the plasma and the red blood cells.
    - Pipette slowly in a circular motion to obtain as many buffy coat cells as possible.

- Contamination of the buffy coat with red blood cells is expected and not a concern. There is no need to further purify the white blood cells with a Ficol separation.

- Snap-freeze cryovials in liquid nitrogen (if available).

- Store cryovials in a -70° C freezer until shipped.

Shipping Instructions

Prior to shipping, the Specimen Submission Form (please email cccp@coh.org for a copy of the form) should be faxed to the Statistical Center at the City of Hope AND the Mack lab (916-734-2361). There must be a completed specimen collection form for each time point collected.

The frozen specimens (along with completed Specimen Submission Forms) should be shipped on dry ice by overnight courier Monday through Wednesday to:

Philip C. Mack, Ph.D.
Division of Hematology/Oncology
University of California, Davis Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817

Contact:
Leslie J. Snyder or Philip C. Mack
Phone: 916/734-3734
E-mail: leslie.snyder@ucdmc.ucdavis.edu

The Federal Guidelines for Shipment are as follows:
- The specimen must be wrapped in an adsorbent material;
- The specimen must be placed in an AIRTIGHT container (resealable bag);
- Pack the resealable bag and specimen in an Styrofoam shipping container along with enough dry ice to last for 2 days;
- Pack the Styrofoam shipping container in a cardboard box;
- The cardboard box must be labeled with a Hazardous Materials label for the Dry Ice.

APPENDIX G - CCCP Registration Procedures for Phase II Trials

1. Registrations for Phase II protocols must be made through the Data Coordinating Center (DCC) office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m. Pacific Time, Monday through Friday (except holidays).
2. Patients must be registered within 5 days (to allow for drug shipment via Priority Mail) prior to initiation of protocol therapy.
3. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the City of Hope Data Coordinating Center (DCC) at (626) 256-HOPE (4673), ***extension 65928.***
4. Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to study calendar/protocol.
5. Patients must sign an informed consent prior to registration.
6. Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.
7. Complete the Eligibility Checklist.
8. Verify that all required prestudy tests were performed.
9. Fax the completed Eligibility Checklist, signed and dated informed consent, pathology report, and relevant laboratory results to the City of Hope Consortium Coordinator for confirmation of eligibility. The FAX number is (626) 256-8654.
10. Call the City of Hope Consortium Coordinator at (626) 256-HOPE (4673), extension 65928 to confirm the FAX arrival. If the Consortium Coordinator is not in the office, have them paged at (626) 423-5365.
11. If the patient qualifies, the City of Hope Consortium Coordinator will call the registering institution to complete the registration/randomization procedure and assign the patient's study ID number.
12. Once a patient has been registered, the Data Coordinating Center will provide a "Confirmation of Registration" to the center registering the patient via email.

For questions regarding eligibility call City of Hope California Cancer Consortium,
Data Coordinating Center
(626) 256-HOPE (4673), extension 65928

APPENDIX H – AMG 386 Dose Rounding Guideline Tables

Table 1.0 Dose Level: 15 mg/kg

Subject's Actual Weight	AMG 386			
		Number of Vials to Dispense		
Weight in kilograms (kg)	AMG 386 dose in milligrams (mg)	150 mg	600 mg	Total number of vials to dispense
25 to 34.9	450	3	0	3
35 to 44.9	600	0	1	1
45 to 54.9	750	1	1	2
55 to 64.9	900	2	1	3
65 to 74.9	1050	3	1	4
75 to 84.9	1200	0	2	2
85 to 94.9	1350	1	2	3
95 to 104.9	1500	2	2	4
105 to 114.9	1650	3	2	5
115 to 124.9	1800	0	3	3
125 to 134.9	1950	1	3	4
135 to 144.9	2100	2	3	5
145 to 154.9	2250	3	3	6
155 to 164.9	2400	0	4	4
165 to 174.9	2550	1	4	5
175 to 184.9	2700	2	4	6
185 to 194.9	2850	3	4	7
195 to 204.9	3000	0	5	5