Amendment

Protocol Number: 12C0079-R **Reference Number:** 365732

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Protocol Title: A Phase II Multicenter Study of AMG 386 and Abiraterone in Metastatic Castration Resistant Prostate Cancer

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: 01/03/2017

Protocol Version Date: 11/15/2016

Abbreviated Title: AMG 386 + abiraterone in mCRPC

CTEP Protocol #: 9068

CC Protocol #: 12C0079 R

Title: A Phase II Multicenter Study of AMG 386 and Abiraterone in Metastatic Castration Resistant Prostate Cancer

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NCI Supplied Investigational Agent:

Drug Name:	AMG 386
IND Number:	114215
NSC Number	751173
Sponsor:	CTEP
Manufacturer:	Amgen

Commercially Available Agents:

Abiraterone and prednisone may be supplied by the NIH Clinical Center pharmacy. Prednisone and abiraterone, if not being provided by the NIH Clinical Center, will be supplied by the local site pharmacy.

PRÉCIS

Background:

- Inhibition of angiogenesis, either as a stand-alone approach or in combination with chemotherapy, has demonstrable antitumor efficacy against castration-resistant prostate cancer (CRPC) and there are several antiangiogenic agents that are now in clinical trials in this population of patients.
- AMG 386 is a novel peptide-Fc fusion protein. The molecule is a non-glycosylated homodimer engineered by fusing an IgG1 Fc domain to 4 copies of an anti-angiopoietin 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.
- Abiraterone acetate is a small molecule that irreversibly inhibits CYP17, a rate-limiting enzyme in androgen biosynthesis, to block residual androgen synthesis in the adrenal gland and tumor cells.
- Previous studies have demonstrated that *in vivo* alterations of testosterone levels regulate the expression of VEGF, FGF, and angiopoietin family members. Dual targeting of the androgen and angiogenic axis represents a novel approach as a potential targeted therapy for patients with metastatic CRPC.

Objectives:

- To estimate the treatment effect as measured by progression free survival (PFS) in patients treated with AMG 386 plus abiraterone/prednisone relative to abiraterone/prednisone alone.

Eligibility:

- Patients with progressive, metastatic CRPC with radiographic evidence of progression after primary therapy (surgery or radiotherapy) and adequate androgen deprivation therapy.

Design:

- This is an open-label, randomized, phase II multicenter trial with a two-part design and a planned accrual of 88 patients.
- An initial run-in phase of AMG 386 will be conducted with 15mg/kg weekly escalating to 30mg/kg weekly to establish the MTD. The decision on declaration of a safe and tolerable dose during this run-in phase will lead to the second part of the study consisting of a randomized comparison of abiraterone/prednisone plus AMG 386 (at the established MTD) vs. abiraterone/prednisone alone.
- AMG 386 will be administered intravenously every week, on days 1, 8, 15 and 22 of each 28-day cycle. Abiraterone acetate will be self-administered once daily by mouth and prednisone will be self-administered by mouth either twice per day at 5 mg per dose or once per day at 10 mg per dose as the patient prefers.

SCHE MA

Run-in phase:

Dose Escalation Schedule	
Dose Level	Dose of AMG 386
Level 1	15 mg/kg IV weekly
Level 2	30 mg/kg IV weekly
At all dose levels, subjects will take: 1000 mg abiraterone daily + prednisone 5 mg twice per day or 10 mg once per day	

Treatment:

Patients will be randomized in a 1:1 distribution to receive:

A: 1000 mg abiraterone PO once daily + prednisone PO 5 mg twice per day or 10 mg once per day

B: 1000 mg abiraterone PO once daily + prednisone PO 5 mg twice per day or 10 mg once per day + AMG 386 IV weekly at the MTD established in the run-in phase

Baseline screening evaluations are to be conducted within 16 days prior to protocol enrollment. Baseline scans and x-rays must be performed 4 weeks prior to protocol enrollment. Patients must be evaluated at the NCI clinic each cycle for treatment continuation.

TABLE OF CONTE NTS

1 OBJECTIVES

1.1 PRIMARY OBJECTIVE

- To estimate the treatment effect as measured by progression free survival (PFS) in patients treated with AMG 386 plus abiraterone/prednisone relative to abiraterone/prednisone alone.

1.2 SECONDARY OBJECTIVES

- To evaluate the overall survival of the enrolled patients and the safety and toxicity profile of the combination
- To assess changes in genetic biomarkers related to androgen and angiogenesis signaling axis and to correlate that with efficacy
- To assess changes in the molecular markers of angiogenesis and circulating tumor cells before (CTCs) and after administration of the combination.
- To determine whether there are changes in AR signaling status in CTCs before and after treatment.
- To determine radiographic progression free survival (rPFS)

2 BACKGROUND

2.1 CASTRATION-RESISTANT PROSTATE CANCER

Prostate adenocarcinoma is the most common malignancy in American men and the second leading cause of cancer-related deaths. Approximately 30-35% of patients will have regional or metastatic disease and an additional 25% will develop metastasis. Androgen-deprivation therapy is the mainstay of treatment for metastatic prostate cancer but nearly all men with metastatic prostate cancer will progress to a castrate-resistant phenotype and exhibit progression of disease.[1,2] Once castrate-resistant prostate cancer (CRPC) develops, responses to second-line treatment with alternative hormonal therapy or chemotherapies are limited, with a median overall survival of approximately 12–18 months. CRPC causes significant morbidity, especially with symptoms of pain from bony metastasis and mortality [3]. Chemotherapies have been studied extensively in the field of prostate cancer and have been disappointing until recently, with the demonstration of improved overall survival of 18.9 months with the use of docetaxel and prednisone over mitoxantrone and prednisone with 16.5 months [4]. The search continues for delivering chemotherapy regimens that yield the best survival outcomes while offering the most palliation in these groups of patients where cure is as yet unattainable. It is for this reason that although the combination of docetaxel and estramustine showed similar survival advantage to docetaxel and prednisone [5], based on fewer side effects, docetaxel and prednisone has become the standard of care in patients with metastatic CRPC (mCRPC) [6], although both treatments are currently FDA-approved for CRPC. The past year saw the addition of two therapies to the CRPC treatment armamentarium. First, therapy with the autologous vaccine sipuleucel-T yielded an improvement in overall survival (OS) compared to placebo in a cohort of docetaxel-naïve mCRPC patients [7]. Second, a study in mCRPC patients with docetaxel-refractory disease

demonstrated an improvement in OS with the novel taxane cabazitaxel compared to mitoxantrone [8]. While cabazitaxel represents the only approved regimen in the second-line treatment setting, the median time to PSA progression with most taxane therapy is limited to about 6-8 months, with many patients progressing thereafter when resistance to therapy ensues [9]. The fact remains that men with this disease are not cured and clearly, new therapeutic strategies are needed in patients with advanced CRPC.

2.1.1 Angiogenesis in CRPC

Inhibition of angiogenesis, either as a stand-alone approach or in combination with chemotherapy, has demonstrable antitumor efficacy against CRPC and there are several antiangiogenic agents that are now in clinical trials in this population of patients. The vast majority of antiangiogenic agents being utilized in the clinical setting are based on strategies that either interfere with pro-angiogenic ligands or block signaling of pro-angiogenic receptor tyrosine kinases. An open-label phase II study of thalidomide in CRPC showed a total of 28% of the patients having a greater than 40% decline in PSA [10]. In a subsequent phase II trial of thalidomide plus docetaxel versus docetaxel alone in metastatic CRPC [11], the combination arm showed improvements in PSA response, median progression-free survival (PFS) and median OS [11,12]. At the NCI, a phase II trial using combination therapy with bevacizumab, thalidomide, docetaxel and prednisone in patients with metastatic CRPC has resulted in a 90% biochemical response rate, overall response rate in measurable disease of 64% and a median OS rate of 28.4 months [13]. When considered in the context of historical data showing a median OS of 19.2 months with docetaxel and prednisone alone in patients with CRPC [14], this data suggests that the addition of angiogenesis-targeted agents would be beneficial in this patient population. However, recent results from the phase III CALGB 90401 trial investigating bevacizumab in combination with docetaxel and prednisone in treatment-naïve mCRPC showed improvements in PFS not OS; however, the combination therapy was associated with greater morbidity and mortality. Moreover, a phase IIIa trial of the tyrosine kinase inhibitor sunitinib (plus prednisone), which targets intracellular signaling triggered by the VEGF and PDGF receptors, in patients with advanced CRPC has been halted for lack of efficacy. While these studies validate the potential for an antiangiogenic approach to CRPC, they also indicate the need to investigate alternative ways to target the tumor vasculature and the need for a combination treatment approach. Of particular interest are agents that can target unique mechanisms for tumor angiogenesis, have a better risk-benefit profile, have activity in tumors resistant to existing therapies, and could even be combined with other novel targeted therapies to enhance efficacy and limit the development of resistance.

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 (Ang2) peptide. AMG 386 sequesters Ang1 and Ang2, thereby preventing their interaction with the Tie2 receptor 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.[15]

Angiopoietins as targets of anticancer therapy

The Ang family has four members (Ang 1-4), with Ang1 and 2 being the best understood.[16-19] 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 vascular endothelial growth factor (VEGF).[20] 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.[21] Overexpression of Ang was found to be associated with lymph node metastases in early gastric[22] or breast cancers.[23] 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,[24,25] cardiomyocytes, and tumor cells,[26] 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.[27] 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.[28] In tumor xenograft models, TEMs purified from human tumor specimens markedly promoted angiogenesis, suggesting a potentially critical role of TEMs in human cancer progression.[28-30]

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,[31] 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.[32] 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.[33]

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,[34,35] glioma, gastric cancer,[22,36] breast cancer, bladder cancer,[37,38] and acute myeloid leukemia (AML).[39,40] 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.[16]

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.[15]

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).[15]

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.[41]

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.[15]

Preclinical pharmacology: Pharmacokinetics (PK) studies were conducted in Sprague-Dawley rats and cynomolgus monkeys.[15] 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 length 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.[15]

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.[15]

PK, immunogenicity, and maximum tolerated dose (MTD) in humans: In the phase 1 Study 20040169[42], 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[42]. Population PK modeling in several studies has identified baseline creatinine clearance (CrCl) as a significant covariate for AMG 386 clearance.

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 co-administration.

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 AMG 386.

At doses up to 30 mg/kg weekly in the first-in-human phase 1 Study 20040169[42] 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),[42,43] the post-treatment effects of AMG 386 were assessed by DCE-MRI and 18F-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., ≥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)[42]. 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.[44] 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 AMG 386 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 overall response rate (ORR) was 19%, 37%, and 27% in the AMG 386 3 mg/kg, 10 mg/kg, and placebo groups, respectively.[45] PK analysis revealed a significant correlation between AMG 386 exposure and efficacy.[46] 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%). For the 30 subjects who received open-label AMG 386 in the crossover arm of the study, median PFS was 3.5 months.

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/m2 and capecitabine 1000 mg/m2 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 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.

Results from run-in part of current trial

Enrollment in the run in phase of this study was completed as of Amendment F. Nine patients with mCRPC were enrolled to receive AMG 386 at 2 escalating dose levels (dose level 1 – 15 mg/kg IV weekly; dose level 2 – 30 mg/kg IV weekly) in combination with 1000 mg abiraterone PO once daily + 5mg PO prednisone twice daily. Three patients were enrolled at dose level 1

with no DLTs. Of the 6 patients enrolled at dose level 2, one patient experienced a DLT of grade 3 confusion of 1 week duration. After resolution to baseline, the event did not recur. There were no other grade 3 or greater adverse events attributed to the study agent.

AMG 386 Safety Profile

At the time of study-respective data cutoff dates for safety and efficacy data,[15] 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.[15]

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[42] and Study 20060212).

A unique adverse effect of AMG 386 is edema, which is believed to be due to the target effect on the lymphatic system. AMG 386 does not appear to cause hypertension as typically observed with anti-VEGF agents. 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.[21] 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. Most 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**. None of the events of ascites have had fatal outcomes.

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 in 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 grade 1 or 2 severity. 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 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 pegylated liposomal doxorubicin (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 hemorrhagic 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 hemorrhagic event with the highest incidence overall was epistaxis; incidence varied among studies, from 0% in Study 20040169[42] (AMG 386 monotherapy) to 49% in the blinded arms of Study 20060341 (AMG 386 or placebo in combination with paclitaxel and bevacizumab).

Five fatal hemorrhagic events of 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 drug: 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,[47] 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 pulmonary embolism. In most of the five unblinded studies, the incidence of pulmonary embolism was lower 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)	FORFIRI
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 ABIRATERONE/PREDNISONE

Abiraterone acetate, a pregnenolone analog, is a small molecule that irreversibly inhibits CYP17, a rate-limiting enzyme in androgen biosynthesis, to block residual androgen synthesis in the adrenal gland and tumor cells. CYP17 plays a key role in testosterone biosynthesis, functioning in the conversion of pregnenolone to 17-alpha-hydroxypregnenolone (via a 17-alpha-hydroxylase), and in the subsequent conversion of this moiety to dehydroepiandrosterone (DHEA) via a 17, 20-lyase [48]. In its early development, abiraterone was noted to block testosterone biosynthesis in *in vivo* models at nanomolar concentrations [49]. In a series of phase II studies, abiraterone demonstrated clinical efficacy in both chemotherapy-naïve and docetaxel-treated patients [50-54]. The encouraging data from these early trials resulted in the design of phase III studies.

COU-AA-301, a phase III trial in CRPC, was initiated in April 2008 and randomized a total of 1195 patients with docetaxel-refractory CRPC to either abiraterone or placebo in a 2:1 fashion (both arms received concomitant prednisone therapy) [55]. Patients were stratified by ECOG performance status (0-1 vs. 2), number of lines of prior chemotherapy (1 vs. 2), pain score, and the nature of progression (defined by prostate-specific antigen, radiograph, or both). The primary endpoint of the study was OS, and secondary endpoints included time to PSA progression (TTPP), PSA response rate (PSA RR), and radiographic progression-free survival (rPSF). On August 2010, following the first planned interim analysis, an independent data monitoring committee recommended that the study be unblinded.[56] At this point, abiraterone-treated patients had received a median of 8 cycles of therapy, compared to a median of 4 cycles of placebo in the control arm. Treatment with abiraterone resulted in an improvement of OS from 10.9 to 14.8 months (HR 0.65, 95%CI 0.54–0.77; $P < 0.0001$), and this benefit appeared across multiple subgroups. Abiraterone therapy also yielded superior outcomes with respect to TTPP (10.2months vs. 6.6 months, $P < 0.0001$), rPFS (5.6 months vs. 3.6 months, $P < 0.0001$), and PSA RR (confirmed: 29.1% vs. 5.5%, $P < 0.0001$). The overall frequency of adverse events amongst placebo-treated patients exceeded that amongst abiraterone-treated patients. However, several grade 3/4 toxicities did occur more frequently with abiraterone therapy, including fluid retention (2.3% vs. 1.0%), hypokalemia (3.8% vs. 0.8%), hypertension (1.3% vs. 0.3%), and cardiac disorders, defined as ischemic heart disease, myocardial infarction, supra-ventricular tachyarrythmias, ventricular tachyarrythmias, cardiac failure and possible arrhythmia related signs and symptoms (4.1% vs. 2.3%).

The phase III mCRPC trial, COU-AA-302, randomized 1088 pre-docetaxel mCRPC patients to either abiraterone or placebo in a 1:1 fashion (both arms received concomitant prednisone therapy). The co-primary endpoints of the study were radiographic progression-free survival (rPFS) and OS. At an interim analysis (43% of total events) the Independent Data Monitoring Committee concluded that the OS, rPFS favored the abiraterone arm and unanimously recommended unblinding the study and crossing patients from placebo to abiraterone[57]. At this time, the median follow up was 22.2 months. The median rPFS (HR 0.43, $P<0.0001$) and OS (HR 0.75, $P<0.0097$) were not reached in the abiraterone arm but they were 8.3 months and 27.2 months in the placebo arm, respectively. Several grade 3 or grade toxicities occurred more frequently in the abiraterone arm than in the placebo arm, including: hypertension (3.9% vs.

3.0%); hypokalemia (2.4% vs. 1.9%); ALT increased (5.4% vs. 0.7%); AST increased (3.0% vs. 0.9%.)

Several ongoing trials are examining the agent in earlier settings (i.e., small studies in combination with radiation therapy or as neoadjuvant pre-surgery for localized disease).

2.4 RATIONALE

Ang2 is expressed in prostate cancer bone, liver, and lymph node metastases.[58] In preclinical studies, the administration of L1-10, a peptide-Fc fusion that inhibits interactions between Ang2 and its receptor Tie2, decreased tumor volume and serum prostate-specific antigen (PSA), and increased survival in SCID mice bearing subcutaneous LuCaP 23.1 tumors. Histomorphometric analysis showed a further significant decrease in tumor epithelial area within the L1-10 treated LuCaP 23.1 subcutaneous tumors (P=0.0063), suggesting that inhibiting Ang2 activity impedes angiogenesis and growth of LuCaP 23.1 PCa xenografts.[59] Ang2 expression was significantly correlated to histological grade, vascular density, metastases, and to cancer specific survival in prostate cancer tissues.[60] Moreover, Ang1 induced sprouting angiogenesis in PC3 tumors. Ang1 enhanced angiogenesis and resulted in tumor growth in the case of PC3 tumors.[61] Based on these data, the angiopoietin signaling axis is an important regulator of angiogenesis in prostate cancer. Indeed, in the phase I study of AMG 386, a peptibody that binds to and inhibits Ang1 and Ang2, in combination with chemotherapy in patients with advanced solid tumors, one patient with prostate cancer achieved a partial response in the AMG 386/docetaxel cohort.[62]

Previous studies have demonstrated that *in vivo* alterations of testosterone levels regulate the expression of VEGF, FGF, and angiopoietin family members.[63] VEGF-A and angiopoietins are required for the vascular response to androgens. Androgens stimulate the expression of VEGF through activation of hypoxia inducible factor (HIF). Androgen deprivation therapy (ADT) is associated with lower HIF1a gene expression in human prostate cancer tissue.[64] Another study found a significant decrease in Ang1 and Ang2 following radical prostatectomy in prostate cancer patients.[65] Recent studies examined the effect of androgen deprivation therapy (ADT) on angiogenic factors and showed that CRPC is associated with elevated levels of VEGF and Ang2.[66] Plasma levels of VEGF decreased after ADT, and increased again at time of tumor relapse. In preclinical studies of mice that were xenografted with LNCaP cells, castrated, and administered bicalutimide, our laboratory found that following castration and AR blockade, a very strong correlation existed between the expression of genes involved in hypoxia (i.e., VEGF, HIF1A) and genes involved in androgen receptor signaling (i.e. AR, FKBP5, and PSA) via quantitative PCR (R^2=0.82; P<0.00001) (Figg and Dahut; unpublished observations). Thus, it appears that ADT induces a relationship between factors involved in AR signaling and hypoxia-mediated tumor angiogenesis. As such, inhibition of persistent androgen production and AR-mediated signaling are relevant therapeutic strategies for CRPC.

Dual targeting of the androgen and angiogenic axis represents a novel approach as a potential targeted therapy for patients with metastatic CRPC. We hypothesize that AMG 386 in

combination with abiraterone will be safe, well-tolerated, and effective in patients with metastatic CRPC.

To date, a total of 34 of patients have been accrued. In the randomized portion of the study, 25 patients have been accrued (14 patients at the NCI and 11 patients at Fox Chase Cancer Center). Eleven patients have been randomized to abiraterone/prednisone and 14 patients have been randomized to abiraterone/prednisone plus AMG 386. The MTD of AMG386 is 30 mg/kg IV weekly in combination with abiraterone.

2.4.1 CHAARTED Trial (Rationale for Modification of Exclusion Criteria)

High-volume hormone-sensitive metastatic prostate cancer has historically been treated using hormonal therapy followed by chemotherapy. The disease however remained poorly prognostic in nature. A shift in the treatment paradigm of these patients occurred with the results of the Eastern Cooperative Oncology Group (ECOG) phase III randomized CHAARTED trial, which looked at whether the addition of upfront chemotherapy to hormonal therapy improved overall survival in patients with hormone-sensitive metastatic prostate cancer.

A retrospective subanalysis from this trial was reported by Dr. Christopher Sweeney from the Dana Farber Cancer Institute, at the 2014 American Society of Clinical Oncology (ASCO) Plenary Session.[67] In the CHAARTED trial, men with metastatic castrate-sensitive prostate cancer were randomized 1:1 to receive androgen deprivation therapy (ADT) alone or to ADT with chemotherapeutic drug docetaxel at 75 mg/m2 every 3 for 6 cycles to be started within 4 months of starting ADT. ADT plus docetaxel resulted in a median overall survival of 57.6 months (HR= 0.61; P = .0003) compared to 44 months in the ADT arm1. Patients were stratified according to high-volume vs low-volume disease and the benefit for docetaxel therapy was found to be more apparent in the high-volume metastatic group vs the low-volume metastatic group. In the ADT plus docetaxel arm of the trial (n=397), common grade 3 non-hematologic toxicities include allergic reaction (3%) and fatigue (4%); common grade 4 toxicities include thrombo-emobolism (1%) and allergic reaction (<1%). Common grade 3 hematologic toxicities include neutropenia (3%) and febrile neutropenia (4%); common grade 4 toxicities include neutropenia (9%) and febrile neutropenia (2%).

Given the very positive results of the CHAARTED trial and current shift towards initial treatment with docetaxel for high-volume hormone-sensitive metastatic disease, we propose amending protocol 12-c-0079 to address this change in the treatment paradigm. Patients may be enrolled onto protocol 12-c-0079, if they received docetaxel chemotherapy for metastatic castrate-sensitive prostate cancer. Patients are excluded if they have been treated with docetaxel chemotherapy for metastatic castrate-resistant prostate cancer. A patient will not be enrolled if he progressed during docetaxel chemotherapy, as this represents a different population of patients than those being evaluated in this trial. A time period of 6 months will be required between a patient's completion of the 6th cycle of docetaxel until the first dose of study treatment (cycle 1, day 1). This time period is based upon data seen in other solid tumor types, such as retreatment in ovarian cancer with platinum based chemotherapies, and this is a reasonable amount of time for patients to have recovered from toxicity from docetaxel.

2.5 CORRELATIVE STUDIES BACKGROUND

2.5.1 Genetic Biomarkers

Polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism (RFLP) or direct sequencing will be used to genotype a single nucleotide polymorphism (SNP) in Ang2 (variant T allele in rs1868554), which was shown to be associated with a variation in plasma ANG2 isoforms.[68] We will characterize this ANG2 isoform variation and expression and investigate its effects in CRPC and in response to AMG 386 therapy. Genotyping will also be performed on a specific CYP17 lyase SNP (variant A allele in rs10883783) which was shown to be associated with a 56% reduction in prostate cancer-specific mortality.[69]

2.5.2 Angiogenic Biomarkers

Plasma will be obtained to measure changes in the molecular markers of angiogenesis before and after administration of the combination since previous studies have found a significant decrease in Ang1 and Ang2 following radical prostatectomy in prostate cancer patients. [65] In patients treated with pre-operative ADT, significant correlation was noted among AR, HIF1a, VEGF-A, and VEGF-C, demonstrating that ADT is associated with lower HIF1a gene expression in prostate cancer tissues and documents prognostic value for VEGF-A and VEGF-C expression levels.[64] Induction of plasma angiogenic factors, VEGF and PlGF, is characteristic for anti-angiogenic agents targeting VEGF or VEGFR2. In this study, the effects of AMG 386 on both plasma VEGF and PlGF will be evaluated, which serve as the pharmacodynamics markers. We will thus elucidate the relationship between biomarker expression, treatment response, and biologic behavior. We will assess the effect of AMG 386 on modulating these angiogenic factors in the CRPC setting in hopes of identifying a biomarker signature and determine whether abiraterone and AMG 386 produce a synergistic or additive effect in modulating plasma levels of these angiogenic factors.

2.5.3 Predictive biomarkers: Circulating tumor cells (CTCs) and AR signaling

CTCs will be evaluated before and after drug administration as changes in CTC counts were shown to correspond with changes in PSA for patients treated with abiraterone.[53] CTC enumeration at baseline and post-treatment is prognostic of survival and the shedding of cells into the circulation represents an intrinsic property of the tumor, distinct from extent of disease. Molecular determinants can be identified and characterized in CTCs as potential predictive biomarkers of tumor sensitivity to therapeutic treatments. CTC will also be isolated pre-drug and immediately following the initial doses of abiraterone. Genetic analysis will be performed to determine the relative levels of androgen receptor (AR), an indicator of gene amplification; the relative activity of AR, a marker for AR activity that may infer functional change and gene mutations; and the ability of abiraterone to regulate the transcription activity of AR in the circulating tumor cells. These markers directly inform the nature of genetic changes on AR in CRPC and the ability for abiraterone to affect AR activity and associated pathway. Also, as TMPRESS2-ERG is the most common driver oncogene translocation downstream of AR, occurring in nearly half of the CRPC patients, this translocation will be examined. Correlative studies will be performed between the above biomarkers and clinical responses including PFS to delineate the biomarkers predictive of response to abiraterone.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria

3.1.1.1 Must have metastatic, progressive, castrate-resistant prostate cancer (CRPC) with radiographic evidence of disease that has continued to progress radiographically or biochemically (rising PSA levels on successive measurements) despite adequate androgen-deprivation therapy. If patients had been on flutamide, disease progression is documented 4 weeks or more after withdrawal. For patients on bicalutamide or nilutamide disease progression is documented 6 or more weeks after withdrawal. Flutamide, nilutamide and bicalutamide disease progression requirements only apply to patients who have been on these drugs for at least the prior 6 months.

3.1.1.2 Histopathological confirmation of prostate cancer by the Laboratory of Pathology of the NCI or Walter Reed National Military Medical Center prior to entering this study. Patients enrolled at participating sites may have histopathological confirmation at the enrolling centerprior to entering the study. Patients whose pathology specimens are no longer available may be enrolled if the patient has a clinical course that is consistent with prostate cancer and available documentation from an outside pathology laboratory of the diagnosis. All efforts should be made to have the material forwarded to the research team for use in correlative studies in cases where original tissue blocks or archival biopsy material is available.

3.1.1.3 Patients must have metastatic disease, defined as at least one lesion on bone scan or 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.

3.1.1.4 Patients participating in the study must have mCRPC.

3.1.1.5 Patients who have received docetaxel plus ADT for metastatic castrate sensitive prostate cancer are eligible for the study. (Patients may enroll as long as they did not have progressive disease while on docetaxel and are 6 months removed from treatment, with all treatment related toxicities resolving to at least grade 1.)

3.1.1.6 Patients may not have had more than 7 days of treatment with ketoconazole by mouth in the past 6 months.

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

3.1.1.8 ECOG performance status ≤ 2 for run-in phase; ECOG ≤ 1 for randomized phase (see **Appendix A**)

3.1.1.9 Life expectancy of > 3 months for the run in phase and > 6 months for the randomized phase

3.1.1.10 Adequate bone marrow, hepatic, and renal function with:

leukocytes	≥ 3000/μL

ANC	≥ 1500/μL
Platelets	≥ 100000/μL
Total bilirubin	≤ 1.5 X institutional upper limits of normal
AST (SGOT)/ALT (SGPT)	≤ 2.5 X institutional upper limits of normal
PTT or aPTT	≤ 1.5 X ULN per institutional laboratory range and INR ≤5
creatinine	≤ 1.5 X institutional upper limits of normal
	OR
creatinine clearance of	>40 mL/min per 24 h urine collection or calculated according to the Cockcroft-Gault formula

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

urinary protein	≤30 mg/dL in urinalysis or ≤1+ on dipstick, unless quantitative protein is <1000 mg in a 24h urine sample

3.1.1.11 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

3.1.1.12 Must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be ≤ grade 1 CTCAE version 4 or has returned to baseline. Alopecia > grade 1 is permitted.

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

3.1.1.14 Must have the ability to understand and the willingness to sign a written informed consent document.

3.1.2 Exclusion Criteria

3.1.2.1 Patients who have had chemotherapy for metastatic castration-resistant prostate cancer.

3.1.2.2 History or presence of known central nervous system metastases.

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

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

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

3.1.2.6 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.

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

3.1.2.8 Minor surgical procedures, placement of tunneled central venous access device within 3 days prior to randomization/enrollment.

3.1.2.9 Treatment within 30 days prior to enrollment with the following: cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, methotrexate, azathioprine, rapamycin, and targeted immune modulators such as abatacept (CTLA-4-Ig), adalimumab, alefacept, anakinra, belatacept (LEA29Y), efalizumab, etanercept, infliximab, or rituximab.

3.1.2.10 Patients who have had large field radiotherapy must wait 2 weeks prior to entering the study.

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

3.1.2.12 Contraindication to steroid use or history of allergic reactions attributable to the study compounds.

3.1.2.13 History of allergic reactions to bacterially-produced proteins.

3.1.2.14 Previously diagnosed with another malignancy, within the past two years with the exception of non-melanoma skin cancers or non-invasive bladder cancer.

3.1.2.15 Patients who have not yet completed at least 28 days (30 days for prior monoclonal antibody therapy) since receiving other investigational drugs.

3.1.2.16 Inability to absorb abiraterone after oral administration (i.e., previous major gastrointestinal surgery or gastrointestinal disease resulting in malabsorption).

3.1.2.17 Use of ketoconazole, itraconazole, ritonavir, cyclosporine, carbamazepine, phenytoin, phenobarbital within 2 weeks prior to and while on study therapy.

3.1.2.18 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the study agents. 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.

3.1.2.19 Uncontrolled intercurrent illness or infections, unstable angina pectoris, cardiac arrhythmias, renal dysfunction, or psychiatric illness/social situations that would limit compliance with study requirements.

3.1.2.20 Have had treatment with docetaxel for the treatment of metastatic castrate-sensitive prostate cancer within 6 months before the first dose of study enrollment.

3.1.2.21 Have had progression of prostate cancer on prior docetaxel treatment for castrate sensitive disease.

3.1.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Women are excluded as prostate cancer does not exist in this population.

3.1.4 Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	0	+	4	=	4
Not Hispanic or Latino	0	+	84	=	84
Ethnic Category: Total of all subjects	0 (A1)	+	88 (B1)	=	88 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	1	=	1
Asian	0	+	2	=	2
Black or African American	0	+	13	=	13
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	0	+	71	=	71
Racial Category: Total of all subjects	0 (A2)	+	88 (B2)	=	88 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 3 pts/month **Total Accrual:** **Expected** 76 Min 88 Max

3.2 SCREENING EVALUATION

This does not include the baseline correlative studies that will only be performed after the patient has signed the consent form.

- To be performed 1 week prior to enrollment
  - History and physical exam including weight and vital signs

- Tumor marker profile: PSA

➢ To be performed within 16 days prior to enrollment

- CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time
- urine analysis with dipstick
- Electrolytes, BUN, creatinine, urine protein-creatinine ratio (UPC), glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH

➢ To be performed within 4 weeks prior to enrollment

- CT scan of chest, abdomen, and pelvis
- Technetium 99 bone scintigraphy scan

4 REGISTRATION AND RANDOMIZATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

For participating site Registration:

All patients must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. A protocol registration form and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject after the participant has signed consent, complete the top portion of the form and fax to the CRO at 301-480-0757. Once eligibility is confirmed, complete the remainder of the form which is the eligibility checklist and fax the completed registration checklist to the CRO at 301-480-0757. The CRO will notify you either by e-mail or fax that the protocol registration form has been received. The CRO will assign a unique patient/subject ID number for each eligible subject that will be used to enter data into the C3D data base. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Guinevere Chun, 301-443-4147, gchun@mail.nih.gov. Technical questions about the form should be directed to the Central Registration Office (301-402-1732).

4.1 RANDOMIZATION (OR STRATIFICATION) PROCEDURES

Patients participating in the treatment part will be randomized in a 1:1 distribution to receive:

A: 1000 mg abiraterone PO once daily + PO prednisone 5 mg twice per day or 10 mg once per day **B:** 1000 mg abiraterone PO once daily + PO prednisone 5 mg twice per day or 10 mg once per day + AMG 386 IV weekly at 30 mg/kg, the MTD established as of Amendment F.

Randomization will be stratified according to prior ketoconazole or enzalutamide use. Stratification will be performed by the Central Registration Office.

5 TREATMENT P LAN

This study will be performed in two parts. In the first part, a safety run-in of AMG 386 will be conducted with 15mg/kg weekly escalating to 30mg/kg weekly. The decision on declaration of a safe and tolerable dose during part 1 will lead to part 2 consisting of a 70- patient randomized comparison of abiraterone/prednisone plus AMG 386 to abiraterone/prednisone. As of amendment F, the randomized dose of AMG 386 was established as 30 mg/kg.

The first part of this study is a standard 3+3 dose escalation with the primary objective of establishing the MTD for AMG 386 when given in combination with standard-dose abiraterone acetate/prednisone. Abiraterone acetate will be taken orally at a dose of 1000 mg once daily and prednisone will be taken orally at a dose of either 5 mg twice per day or 10 mg once per day. AMG 386 will be administered as an intravenous infusion every week. The AMG 386 dose will be escalated in cohorts of 3 to 6 patients up to a maximum of 30 mg/kg weekly (see table below).

Each cohort in the run-in part of the study is planned to have at least 3 patients to evaluate for toxicity. Three patients will be treated at a given dose level and observed for acute toxicity for one course of treatment before any more patients are entered. Toxicities will be graded using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

- If none of the three patients at a given dose level experience dose-limiting toxicity (DLT), accrual will proceed to the next cohort.
- If one of three patients treated at a dose level experiences DLT that is considered to be at least possibly related to AMG 386, then three more patients will be enrolled at that same level. If the incidence of DLT among those six patients is one in six, then the next cohort of three patients will be treated at the next higher dose.
- In general, if two or more of the six patients treated at a dose level experience DLT, then the MTD is considered to have been exceeded. The MTD is defined as the highest dose studied for which the incidence of DLT was less than 33%. However, data from the run in part will be reviewed by the study team and the sponsor (CTEP) before initiation of the second part to finalize the determination of the phase 2 dose.
- For MTD determination, dose-limiting toxicities will be evaluated throughout the first 28 days of treatment (Cycle 1). Patients who exit the study for reasons other than drug-related toxicity prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment of each cohort. If at the first dose level more than two DLTs in six subjects are observed, then the study will be stopped.

5.1 AGENT ADMINISTRATION

Treatment will be administered on an outpatient basis. 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.

Run in part to establish MTD:

Dose Escalation Schedule	
Dose Level	Dose of AMG 386
Level 1	15 mg/kg
Level 2	30 mg/kg

REGIMEN DESCRIPTION					
Agent	***Premedication; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
AMG 386	none	** in 50 or 100 cc 0.9% Normal saline (see sections **5.1.1** & **8.1**)	IV infusion pump over 60 minutes	Days 1, 8, 15, 22*	*28 days* *(4 weeks)*
Abiraterone	No food should be consumed for at least 2 hours before and for at least 1 hour after dose	1000 mg (4 tablets)	PO	Daily	
Prednisone	Take with food or with milk to reduce stomach irritation.	5mg or 10 mg	PO	Twice per day or Once per day	
** +/- 5 days* ***Doses as appropriate for assigned dose level.*					

5.1.1 AMG 386

AMG 386 dose will be calculated using the subject's actual body weight (Kg). The baseline weight (Kg) 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 tables that are currently available in the protocol (directly below this paragraph). All calculated dose in dose levels 10 mg/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 B for dose rounding guidelines that use 150 mg and 600 mg vials. AMG 386 calculated doses are based on weight strata as outlined in the table below until the 240 mg supply has been depleted. The actual doses of AMG 386 based on the subject's weight will be given in increments of 150 mg (300 mg [for 30 mg/kg dosing]) as outlined in the table below:

Subject's actual weight	AMG 15 mg/kg	AMG 30 mg/kg
Weight in kilograms (kg)	AMG 386 dose in milligrams (mg)	AMG 386 dose in milligrams (mg)
35 to 44.9	600 mg	1200 mg
45 to 54.9	750 mg	1500 mg
55 to 64.9	900 mg	1800 mg
65 to 74.9	1050 mg	2100 mg
75 to 84.9	1200 mg	2400 mg
85 to 94.9	1350 mg	2700 mg
95 to 104.9	1500 mg	3000 mg
105 kg and above	Add 150 mg AMG 386 for each additional 10 kg in subject's weight	Add 300 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 CRF.

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 should 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 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. The subject may develop a reddened area around the site of infiltration which is caused by accumulation of investigational product in the surrounding tissues (depot effect). There is no specific treatment for extravasation of AMG 386. Supportive therapies may be indicated at the discretion of the investigator. The remaining volume of AMG 386 may be administered through a separate IV well away from the area of extravasation.

5.1.2 Abiraterone

A 1,000 mg dose of abiraterone should be taken orally once daily. Abiraterone must be taken on an empty stomach, preferably in the morning. If a dose of abiraterone is missed, patients should be instructed to take the dose at any time during the day. No food should be consumed for at least two hours before the dose of abiraterone is taken and for at least one hour after the dose of abiraterone is taken. Patients should not take two doses on the same day.

Pill counts will be maintained by study personnel.

5.1.3 Prednisone

Prednisone should be taken orally either, at 5mg twice a day for each dose or 10 mg once a day as is the patient's preference. Prednisone should be taken at approximately the same time every day. The doses should be taken about 12 or 24 hours apart ± 2 hours depending on which dosing regimen is used. Gastric irritation may be reduced if taken before, during, or immediately after meals or with milk. If a dose of prednisone is missed (more than 14 hours [twice daily regimen] or 36 hours [once daily regimen] have passed since the last dose), patients should be instructed not to make up the dose and to resume taking prednisone at the next scheduled dose.

5.2 DEFINITION OF DOSE-LIMITING TOXICITY

Dose limiting toxicities (DLTs) are defined as any grade 3 or higher hematologic (excluding anemia) or non-hematologic toxicity considered to be possibly related to AMG 386. Furthermore, any treatment related AEs that lead to reduction of dose exposure of either agent (duration or dose) by > 50% in cycle 1 will be considered a DLT. Anemia will not be considered as a DLT. Three patients must complete at least 1 cycle of therapy prior to considering dose escalation in the next cohort of patients. Determination of DLT for the purpose of dose escalation enrollment will be based on toxicities observed in the first 28 days of treatment (cycle 1) and must be considered as at least possibly related to study drug. Evaluation for toxicity will continue throughout the study and should dose limiting toxicities occur beyond the cycle one, consideration will be given to halting the dose escalation and studying the lower dose level.

Management and dose modifications associated with the above adverse events are outlined in Section **6**.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**

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

If ≥2 patients experience a DLT at any dose level, at any time in during the run-in part, then subsequent patients will be enrolled at the next lower dose level.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of abiraterone acetate 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.

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. (See **Appendix C** for list of CYP2D6 substrates).

Abiraterone acetate is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. The following medications will be excluded prior to and during the study if indicated: ketoconazole, itraconazole, ritonavir, products containing grapefruit juice, cyclosporine, carbamazepine, phenytoin, phenobarbital and prophylactic use of G-CSF, GM-CSF.

Abiraterone acetate has the ability to inhibit a variety of liver metabolic enzymes in vitro. The clinical impact of this inhibition in humans taking drugs metabolized by these enzymes is unknown. Therefore, all patients enrolled onto this trial who are taking concomitant medications that are known to be metabolized by the liver should be closely observed for side effects of these concomitant medications. Furthermore, patients taking narrow therapeutic index medications, (e.g. warfarin, quinidine, or digoxin) should be monitored proactively .

5.4 DURATION OF THERAPY

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- 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 overall survival only after removal from study treatment or until death, whichever occurs first. Follow-up will be annual telephone contact to assess survival status and to collect available information on post study anti-cancer therapy. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index). Patients removed from study therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

5.6.1 Criteria for removal from protocol therapy

- Progressive disease
- Intercurrent illness that prevents further administration of treatment
- Participant requests to be withdrawn from active therapy
- Toxicity
- Investigator discretion
- Death

5.6.2 Off Study Criteria

- Participant requests to be withdrawn from study
- Investigator discretion
- Death

5.6.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

5.6.3.1 For Participating Sites

All subjects must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. An off-study form will be supplied by the CCR study coordinator. Send the completed off-study form to the CCR study coordinator.

6 DOSING DELAYS/DOSE MODIFICATIONS

Toxicities will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless otherwise indicated. The following adjustments will only apply if the toxicities reported are attributed by the investigator to be at least probably related to abiraterone or AMG 386. Dose delay and dose reduction will be according to the following rules:

6.1 ABIRATERONE DOSE MODIFICATION

Dose reduction and interruptions will be allowed during the study. Patients who experience a dose-limiting toxicity (DLT) probably related to abiraterone will have their dose held until the toxicities have resolved as outlined in the tables below. Recovery is defined as improvement to grade 1, eligibility value, or baseline value. For selected DLTs, upon re-initiation of treatment with abiraterone, the patient will have their dose reduced to the next lower dose level. Abiraterone may not be held for more than 28 consecutive days. The dose of abiraterone may not be reduced below 750 mg once daily. Should abiraterone be held longer or should any toxicity requiring a dose level reduction occur more than once, the subject will be removed from study therapy.

Table 6-1: Abiraterone dose levels

Dose Level 1	1000 mg PO qd
Dose Level -1	750 mg PO qd

6.1.1 Hematologic Toxicities

In the event of grade 3 or grade 4 hematologic toxicity (excluding anemia) deemed to be related to abiraterone, abiraterone should be suspended until the adverse event resolves to ≤ grade 2. CBC will be checked weekly. Abiraterone will be resumed at the next lower dose level.

6.1.2 Non-Hematologic Toxicities

Treatment with abiraterone should continue uninterrupted for grade 1 non-hematologic toxicities. However, if the symptoms last for more than 7 days and are significantly intolerable to the patient, the dose of abiraterone may be reduced to the next lower dose level.

Grade 2 Non-Hematologic Toxicities

Maintain the dose of abiraterone but treat symptomatically for nausea, vomiting, or diarrhea. The administration of abiraterone may be interrupted in patients with intolerable grade 2 events. Abiraterone should be re-initiated at the same dose when the adverse event resolves to grade 1 or baseline. If the nausea, vomiting, or diarrhea is persistent and intolerable despite symptomatic management, the dose of abiraterone may be reduced to the next dose level. For any other grade 2 toxicity, the dose of abiraterone need not be reduced unless the adverse event is intolerable to the patient.

Grade 3 Edema (as defined in **Table 6-2** below)

In the event of grade 3 edema, abiraterone will be held. Abiraterone should be re-initiated at the same dose level when edema resolves to grade 1 or baseline.

Grade 3 or 4 Other Non-Hematologic Toxicity

Suspend treatment with abiraterone until toxicity improves to grade 1 or pre-treatment baseline then re-initiate treatment at a lower dose. Patients with intolerable or limiting toxicity after one dose reduction will have abiraterone discontinued.

6.2 AMG 386 DOSE MODIFICATION

Patients who experience dose-limiting toxicities (DLT) possibly related to AMG 386 will have their AMG 386 treatment modified as outlined in the tables below. Edema is a known adverse event of AMG 386 and the etiology, which may include, but is not limited to, tumor obstruction of lymphatic or blood vessels, congestive heart failure, iatrogenic fluid overload, renal insufficiency, nephrotic syndrome or other significant hypoalbuminemic states, should be ascertained.

To provide a common framework for reporting edema (including lymphedema), investigators should report edema and manage their subjects as **defined in this section.**

- **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 and generalized edema/lymphedema) **as follows**:

Table 6-2: Edema

Edema/lymphedema (grade based on this table, NOT per CTCAE v4.0)	**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 v4.0 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 below for AMG 386 dose modification guidelines.

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">• There will be no dose reductions for AMG 386, only dose delays.
• In the event that AMG 386 is held for >28 days, 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="3">Edema/lymphedema</td><td colspan="2">Edema should be classified and graded as per instructions above</td></tr>
<tr><td>Grades 1:
(Trace thickening or faint discoloration of the affected area)</td><td rowspan="2">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></tr>
<tr><td></td><td>Grade 3:
[(Severe symptoms that may involve skin blistering or skin breakdown; limitations to activities of daily living (ADL)]</td><td>• Permanently Discontinue AMG386</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**
Pleural effusion and ascites	Non-life-threatening pleural effusion or ascites	• 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 (**Each invasive procedure for pleural effusion or ascites should be documented on CRFs).**
	Grade 4 or Life threatening pleural effusion or ascites	• 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.

Treatment Modification for AMG 386-Related Adverse Events (Based on CTCAE V4.0)		
Event	**CTCAE V4 Grade (unless noted otherwise)**	**Action to be Taken**
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
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.	
	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.

Treatment Modification for AMG 386-Related Adverse Events (Based on CTCAE V4.0)		
Event	**CTCAE V4 Grade (unless noted otherwise)**	**Action to be Taken**
	Severe or life-threatening:	Treat per institutional guidelines. Discontinue AMG386.
	*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.	
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 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.
	Grade 4	If a grade 4 event is considered to be related to AMG 386, the study should be discontinued. Resuming AMG 386 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.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS /DATA AND SAFETY MONITORING PLAN

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 **7.2.1.1**) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR)

7.1.1 CAEPR for AMG 386 (Trebananib, NSC 751173)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1422 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.

Version 2.5, April 18, 2016[1]

Adverse Events with Possible Relationship to AMG 386 (Trebananib) (CTCAE 4.0 Term) [n= 1422]			**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)***
	Infusion related reaction[2,4]		***Infusion related reaction[2,4] (Gr 2)***

Adverse Events with Possible Relationship to AMG 386 (Trebananib) (CTCAE 4.0 Term) [n= 1422]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pain		***Pain (Gr 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		***Allergic reaction***[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, Gastrointestinal hemorrhage, Arterial hemorrhage, Bronchopulmonary hemorrhage, Bladder hemorrhage, Rectal 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 - Acute coronary syndrome; Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (atrioventricular block second degree); Heart failure; Mitral valve disease; Pericarditis; Restrictive cardiomyopathy; 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; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Bloating; Colitis; Constipation; Dysphagia; Enterocolitis; 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]; Fever[4]; General disorders and administration site conditions - Other (generalized edema); Localized edema; Malaise; Multi-organ failure; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (hepatitis toxic)
INFECTIONS AND INFESTATIONS - Abdominal infection; Anorectal infection; Appendicitis; Kidney infection; Lung infection; Sepsis; Skin infection; Upper respiratory 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; Investigations - Other (granulocyte count decreased); 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; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS – Dizziness[4]; Dysgeusia; Dysphasia[4]; Edema cerebral; Encephalopathy; Headache[4]; Ischemia cerebrovascular; Nervous system disorders - Other (hemiplegia); Nervous system disorders - Other (left-sided hemineglect); Paresthesia; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Mania; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury[2]; Hematuria; Urinary tract obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Apnea; Chylothorax; Cough; Dyspnea[4]; Epistaxis; 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; 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 – 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 Adverse Event List(s) for Commercial Agent(s)

7.1.2.1 Abiraterone

(See package insert for complete list of side effects)

Serious adverse events include heart palpitations, lightheadedness, headache, confusion, muscle weakness, edema, leg pain, shortness of breath, blood in urine or problems urinating, liver problems, allergic reaction.

The most common adverse events (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

7.1.2.2 Prednisone

(See package insert for complete list of side effects)

Serious side effects of prednisone include hypertension, hyperglycemia, infections, ruptured tendons, psychotic reactions, glaucoma, severe edema, gastrointestinal bleeding and allergic reactions. Short term side effects may include headaches and insomnia while long term side effects may cause weight gain, exopthalmos, osteoporosis, acne and truncal fat distribution.

7.2 DEFINITIONS

7.2.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.2.1.1 Adverse Event Characteristics:

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

- 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.

7.2.2 Suspected adverse reaction

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

7.2.3 Unexpected adverse reaction

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

7.2.4 Serious

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

7.2.5 Serious Adverse Event (SAE)

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

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

7.2.6 Disability

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

7.2.7 Life-threatening adverse drug experience

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

7.2.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.2.9 Non-compliance (NIH Definition)

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

7.2.10 Unanticipated Problem

Any incident, experience, or outcome that:

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

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 EXPEDITED ADVERSE EVENT REPORTING TO CTEP

7.3.1 Reporting via CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). 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/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section **7.3.4**).

7.3.2 In the event of lost internet connectivity

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.

7.3.3 Multi-institutional studies

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

7.3.4 Expedited Reporting Guidelines

Note: A death on study requires <u>both</u> 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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

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

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

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

NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.4 ROUTINE ADVERSE EVENT REPORTING TO CTEP

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 NCI IRB AND NCI CLINICAL DIRECTOR ADVERSE EVENT REPORTING

7.5.1 NCI-IRB and NCI Clinical Director Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

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

Reports must be received within 7 days of PI awareness via iRIS.

7.5.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

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

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

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

7.5.3 NCI-IRB Reporting of IND Safety Reports

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

7.6 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 48 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

A copy of this form is found in **Appendix** D**.**

7.7 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.

7.8 SECOND MALIGNANCY

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

7.9 DATA AND SAFETY MONITORING PLAN

7.9.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.9.2 Sponsor Monitoring Plan

It is understood that the responsible monitor will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial including CRFs and other pertinent data, provided that subject confidentiality is maintained, and in accord with local requirements.

It will be the monitor's responsibility to inspect the CRF's at regular intervals throughout the study to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator or his/her deputy agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

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)

Classification: Anti-angiopoietin peptibody

M.W.: 63.5 kD

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 a 20 mL and 50 mL vials sizes. 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.

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 classify 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˚ to 8˚C, 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 the IV infusion is completed). The final IV bag must be protected from light if not used immediately.

Do not use vial adaptors when preparing AMG 386 IV solution

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 (i.e., from the time the drug is diluted in 0.9% NS to the time the IV infusion is completed) at ambient temperature, protected from light and must be used within that time.

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 each IV infusion.

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.

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 **12.4**).

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.

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 AGENT(S)

8.2.1 Abiraterone

(Please see package insert for complete drug information)

8.2.1.1 Source: For patient administration oral tablets will be purchased by the local site from commercial sources or may be supplied by the NIH Clinical Center pharmacy.

8.2.1.2 Toxicity: See section **7.1.2.1**

8.2.1.3 Formulation and preparation: Abiraterone is supplied as 250 mg tablets.

8.2.1.4 Stability and storage: Store at 20˚C to 25˚C (68˚F to 77˚F); excursions permitted to 15˚C to 30˚C (59˚F to 86˚F)

8.2.1.5 Administration procedures: See section **5.1.2**.

8.2.1.6 Incompatibilities: Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

Furthermore, based on *in vitro* data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone treatment.

8.2.2 Prednisone

(Please see package insert for complete drug information)

8.2.2.1 Source: For patient administration oral tablets will be purchased by the local site from commercial sources or may be supplied by the NIH Clinical Center pharmacy.

8.2.2.2 Toxicity: See section **7.1.2.2**

8.2.2.3 Formulation and preparation: Prednisone is supplied as 5 mg tablets.

8.2.2.4 Stability and storage: Store at 15 - 30˚C, protected from moisture and light.

8.2.2.5 Administration procedures: See section **5.1.3.**

8.2.2.6 Incompatibilities: Systemic fungal infections and known hypersensitivity to components.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 LABORATORY CORRELATIVE STUDIES

9.1.1 Evaluation of genetic biomarkers of efficacy

Exploratory genetic studies will be performed to identify alleles of known variants such as Ang2 variant T allele and CYP17 lyase variant A allele as well as genes involved in the metabolic pathways of the study drugs as proposed in detail section **2.5.1**. There is substantial germline genetic variability within angiogenesis pathway genes, which may be an important contributor to the heterogeneity of response seen with antiangiogenic therapy. Specifically, this variability has the potential to be used for better selection of patients for future studies evaluating anti-Ang1/2 therapy. Dr. Figg's laboratory has extensive experience and expertise in performing

pharmacogenetic analyses of genes involved in angiogenesis and drug metabolism pathways. Towards this end, polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism (RFLP), direct sequencing, or gene array analysis will be used to genotype the single nucleotide polymorphism (SNP) in Ang2 (variant T allele in rs1868554), which was shown to be associated with a variation in plasma Ang2 isoforms.[68] We will characterize this Ang2 isoform variation and expression and investigate its effects in CRPC and in response to AMG 386 therapy as this potentially could be a resistance mechanism to AMG 386 if the Ang2 variant is not effectively targeted by this agent.

Previous studies have shown that genetic variations in the *CYP17* gene led to increased PCa-specific survival. For example, the CYP17 lyase SNP (variant A allele in rs10883783) has shown to be associated with a 56% reduction in prostate cancer-specific mortality.[69] If these variants alter enzyme activity, then this may have an important impact on the action of CYP17 inhibitors such as abiraterone. Since CYP17 is a crucial enzyme in the testosterone biosynthesis pathway, it remains to be determined whether variant *CYP17* alleles may impair this process, thereby affecting local intracrine testosterone production and subsequent response to anti-androgen therapy. We will determine genetic variants of CYP17 and correlate with clinical outcomes.

Other laboratory correlates will evaluate genotyping of genes involved in the metabolic pathway of these agents to correlate with efficacy.

Pharmacogenetic studies will also be performed to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET). DNA will be analyzed on a DMET Plus (Affymetrix) genotyping platform that tests for 1,936 genetic variations in 225 drug disposition genes, including 47 CYP (phase I metabolism) genes, 13 non-CYP (phase I metabolism) genes, 78 phase II metabolizing genes (including UGTs), 63 transporters, 4 genes involved in facilitation of drug transporters, 9 genes involved in global regulation of drug metabolizing/transporting proteins, 4 drug binding proteins, and 4 drug targets.

9.1.1.1 Collection of Specimen(s)

One 10ml EDTA tube (BD, Franklin Lakes, NJ) will be collected from patients at baseline (after consent, prior to treatment initiation). The sample may be collected at a subsequent visit if missed at baseline.

9.1.1.2 Handling and Processing of Specimens(s)

Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator.

The following information should be provided with each sample. If not on the label, the information may be provided on an inventory sheet linked to the specimen label.

- Patient study ID#
- Sample type
- Date/time of draw (dd/mm/yy 24:00)
- Time point (e.g. C1D1 pre, C1D1 24 hr post)
- Any collection issues (short draw, delayed processing, etc.)

- Protocol title/number
- Institute name
- Contact information

Participating sites should store samples at 4°C until ready for batch shipping (every 4 months).

At NCI site, please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044. Upon arrival in the BPC, genomic DNA will be extracted and analyzed for genetic polymorphisms.

9.1.1.3 Shipping of Specimen(s)

Please email Kathy Compton at comptok@mail.nih.gov prior to shipping on ice to the following address:

NIH/NCI/Molecular Pharmacology Section
Attn: Dr. Figg's Lab
10 Center Drive, Room 5A01
Bethesda, MD 20892

Batched samples should be shipped every 4 months

9.1.1.4 Site(s) Performing Correlative Study

The genotyping will be performed on a research basis in the Molecular Pharmacology Section (Bldg. 10 Room 5A01; William Figg, Pharm D.).

9.1.2 Evaluation of pharmacokinetics (NCI Site only)

Pharmacokinetic (PK) measurements can be correlated with clinical response and toxicity as well as pharmacodynamic (PD) and pharmacogenetic data to possibly identify the plasma concentrations that achieve the best response with least toxicity and to determine if genetics plays a role. CYP17 is the pharmacological target of abiraterone. OATP1B3 is a transporter believed to transport many steroid-based molecules and genotyping may help to shed light on whether abiraterone is a potential substrate.

Bioanalytical measurements will be conducted on an ultra HPLC-MSMS system using a validated assay. The plasma concentration-time data will be analyzed with non-compartmental methods using Phoenix WinNonlin software (Pharsight, Mountain View, CA). The maximum concentration, time to maximum concentration, the area under the curve extrapolated to infinity, volume of distribution and clearance will be calculated. These pharmacokinetic measurements can be correlated with clinical response and toxicity as well as pharmacodynamic (PD) and

pharmacogenetic data to possibly identify the plasma concentrations that achieves the best response with least toxicity and if genetics plays a role.

9.1.2.1 Collection of Specimen(s)

PK samples will be collected at the NCI Clinical Center site only. One 6mL sodium heparin tube (BD, Franklin Lakes, NJ) for the determination of steady-state plasma levels of abiraterone is collected from each patient at the Cycle 2 day 1 visit and the following three visits. The timing of dose administration does not matter in regard to the blood draw. It is important to record the time of blood draw as well as the time the patient took their most recent dose.

9.1.2.2 Handling and Processing of Specimen(s)

Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator. The exact time of each blood draw should be recorded on the tube.

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.
Upon arrival in the BPC, blood samples will be centrifuged for 5 minutes at 1200 x *g* at 4°C. Plasma will be aliquoted into 2 cryovials and stored at -80°C until the time of analysis.

9.1.2.3 Site(s) Performing Correlative Study

The PK measurement and analysis will be performed on a research basis by the Clinical Pharmacology Program (Bldg 10 Rm 5A01; William D. FiggPharm D.).

9.1.3 Determine the biological effects of AMG 386: molecular markers of angiogenesis

Exploratory studies will be performed to determine the impact of AMG 386 combination therapy on serial levels of markers of angiogenesis in order to elucidate the relationship between biomarker expression, treatment response, and biologic behavior as described in further detail in section **2.5.2**. Fluctuations in the levels of angiogenic factors have been detected following an array of anti-angiogenic therapies including bevacizumab, VEGFR2 inhibitors, and their combinations in clinical studies. Recent studies examined the effect of androgen deprivation therapy (ADT) on angiogenic factors and showed that CRPC is associated with elevated levels of VEGF and Ang2.[66] Plasma levels of VEGF decreased after ADT, and increased again at time of tumor relapse, while Ang2 levels were unaffected. It is therefore important to determine the effect of AMG 386 combination therapy on these parameters. Plasma levels of angiogenic factors will be assessed for VEGF, PlGF, bFGF and sVEGFR1 (soluble VEGF receptor 1/sFlt1) as well as Ang1, Ang2, and soluble Tie2. The analyses will be performed with assays developed

in Dr. Liang Cao's laboratory using electrochemiluminescence technology that provides ultra-high sensitivity and very large signal dynamic range. Dr. Cao has extensive experience in biomarker assay development and validation. Purified protein standard will be used for generating standard curves for concentration determination. The currently available ELISA assays do not distinguish AMG 386-bound vs. free Ang1/2; thus, our platform will be tested to detect total Ang1/2 levels in plasma. Data analysis will be performed with Prism (GraphPad, San Diego, CA) to determine the medium value, interquartile range, and *P* value in paired t test. Correlative studies will be performed between the baseline levels of the angiogenic factors and the degree of their change over time with clinical response.

9.1.3.1 Collection of Specimen(s)

One 5mL EDTA plasma tube (BD, Franklin Lakes, NJ) is collected from each patient prior to AMG 386 drug administration at the following four time points: Day 1 of Cycle 1 (baseline, C1D1), Day 15 of Cycle 1 (C1D15), Day 1 of Cycle 2 (C2D1), and Day 1 of Cycle 3 (C3D1).

9.1.3.2 Handling and Processing of Specimens(s)

Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator.

The following information should be provided with each sample. If not on the label, the information may be provided on an inventory sheet linked to the specimen label.

- Patient study ID#
- Sample type
- Date/time of draw (dd/mm/yy 24:00)
- Time point (e.g. C1D1 pre, C1D1 24 hr post)
- Any collection issues (short draw, delayed processing, etc.)
- Protocol title/number
- Institute name
- Contact information

Participating sites should store samples at 4°C until ready for batch shipping (every 4 months).

At NCI site, please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

Upon arrival in the BPC, blood samples will be centrifuged for 5 minutes at 1200 x *g* at 4°C. Plasma will be aliquoted into 2 cryovials and stored at -80°C until the time of

analysis. The samples will be transferred to Dr. Liang Cao's lab at Bldg 37/Rm6134 (301-435-9039) for analysis.

9.1.3.3 Shipping of Specimen(s)

Please email Julie Barnes at julie.barnes@nih.gov prior to shipping on ice to the following address:

NIH/NCI/Molecular Pharmacology Section
Attn: Dr. Figg's Lab
10 Center Drive, Room 5A01
Bethesda, MD 20892

Batched samples should be shipped every 4 months

9.1.3.4 Site(s) Performing Correlative Study

The angiogenic biomarker analysis studies will be performed on a research basis in the laboratory of Dr. Liang Cao (Bldg 37/Rm6134).

9.1.4 Predictive biomarkers for abiraterone: Measurement of circulating tumor cells & androgen receptor pathway analysis

Exploratory studies will be performed to evaluate the levels of circulating tumor cells (CTC) before and after drug administration based on previous abiraterone studies in which CTC counts corresponded with prostate-specific antigen (PSA) levels. (See section **2.5.3**) The clinical utility of monitoring CTC changes with treatment has been demonstrated to be an efficacy-response surrogate biomarker of survival. CTC enumeration is currently being tested in several large phase III trials, including the novel antiandrogen therapies such as abiraterone acetate. Molecular determinants can be identified and characterized in CTCs as potential predictive biomarkers of tumor sensitivity to therapeutic treatments. Recent studies report a significant association between ERG rearrangements in therapy-naive tumors, CRPCs, and CTCs and magnitude of prostate-specific antigen decline (P=0.007) in CRPC patients treated with abiraterone acetate.[76] These data confirm that CTCs are malignant in origin and indicate that hormone-regulated expression of ERG persists in CRPC. CTCs will be investigated as an experimental endpoint using immunofluorescence techniques and CTC identification by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers. Dr. Jane Trepel has extensive experience in working with CTC technology and has developed a platform for accurate detection of CTC enumeration. Dr. Liang Cao is currently developing new CTC technologies capable of isolating live CTC for cancer genetic profiling. His expertise will be needed in this portion of our biomarker studies to assess AR signaling status in CTCs before and after drug treatment and involve cancer genetic profiling that will include the analysis of AR level, activity, and the downstream oncogene TMPRESS2-ERG. We will perform the following statistical analyses: evaluation of the effects of abiraterone in regulating AR activity; correlative analysis between baseline AR activity and clinical outcome; correlative analysis between the reduction of AR activity and clinical outcome; and correlative analysis between TMPRESS2-ERG and clinical outcome.

9.1.4.1 Collection of Specimen(s)

9.1.4.1.1 CTC Enumeration

NCI Site Tubes: Two 7mL EDTA plasma tube (BD, Franklin Lakes, NJ)

Participating Sites Tubes: One 10 mL EDTA plasma tube (BD, Franklin Lakes, NJ) and one 7.5 mL CellSave Preservation tube

Tubes are collected from each patient at the following two time points: prior to AMG 386 drug administration on Day 1 of Cycle 1 (baseline, pre-drug C1D1) and before AMG 386 drug administration on Day 15 of Cycle 1 (pre-drug C1D15). Immediately after collection, invert the blood tubes 8-10 times.

The following information should be provided with each sample. If not on the label, the information may be provided on an inventory sheet linked to the specimen label.

- Patient study ID#
- Sample type
- Date/time of draw (dd/mm/yy 24:00)
- Time point (e.g. C1D1 pre, C1D1 24 hr post)
- Any collection issues (short draw, delayed processing, etc.)
- Protocol title/number
- Institute name
- Contact information

9.1.4.1.2 AR analysis in CTCs (NCI site only)

Two 5 mL EDTA plasma tube (BD, Franklin Lakes, NJ) is collected from each patient at the following two time points: prior to AMG 386 drug administration and before 2pm on Day 1 of Cycle 1 (baseline, pre-drug C1D1) and before AMG 386 drug administration and before 2pm on Day 15 of Cycle 1 (pre-drug C1D15). Immediately after collection, invert the blood tubes 8-10 times. The date and time of each blood draw should be recorded on the tube.

9.1.4.2 Handling and Processing of Specimens(s)

9.1.4.2.1 CTC enumeration:

As soon as possible after the patient is scheduled please send email notification to the Trepel lab: Jane Trepel at trepel@helix.nih.gov; Min-Jung Lee at leemin@mail.nih.gov that the sample is scheduled. After the sample is drawn at the NCI site please call the Trepel lab at 301-496-1547 to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample will be picked up by the lab and processed for CTC enumeration. Participating should ship the samples immediately after collection. See section **9.1.4.3** for shipping instructions.

9.1.4.2.2 AR analysis in CTCs (NCI site only)

As soon as possible after the patient is scheduled please send email notification to the Cao lab: Liang Cao caoli@mail.nih.gov that the sample is scheduled. After the sample is drawn please call the Cao lab (Mr. Yunkai Yu at 301.443.2799) to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample needs to be picked up by the lab within 4 hours. The blood will be processed for CTC isolation.

9.1.4.3 Shipping of Specimen(s)

Specimens for CTC enumeration from participating sites should be shipped immediately at room temperature via FedEx overnight delivery. Please email the Trepel lab: Jane Trepel at trepelj@mail.nih.gov; Min-Jung Lee at leemj@mail.nih.govwith the FedEx shipment tracking number as soon as it is available.

The samples should be sent to the address below:

Jane Trepel
Developmental Therapeutics Branch, NCI
Building 10, Room 12N218
Bethesda, MD 20892
Phone: 301-496-1547

Ship specimens to NCI Laboratory Monday through Thursday only. Do not ship on Fridays, weekends or Federal holidays.

9.1.4.4 Site(s) Performing Correlative Study

The assays will be performed by Dr. Liang Cao's laboratory in the Molecular Targets Core, Genetics Branch, Building 37, Rm 6134 and Dr. Jane Trepel's laboratory Developmental Therapeutics Branch, Building 10, Room 12N230.

9.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered and tracked through the CRIS Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA.

9.2.1 Clinical Pharmacology Program

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP (the Blood Processing Core is part of the CPP). This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at

NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

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

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

10 STUDY CALENDAR

Screening evaluations, x-rays, and scans are to be conducted within the timeframe established in section **3.2**. On study evaluations/procedures with the exception of cycle 1 day 1 (see footnote h) may be performed within ± 5 days of day indicated on calendar. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All follow-up evaluations can be performed during the last week of the prior cycle.

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				Off Therapy Evaluation[k]
Day		1[h]	8	15	22	1	8	15	22	1	8	15	22	
AMG 386 [a]		X	X	X	X	X	X	X	X	X	X	X	X	
Abiraterone acetate/prednisone		Daily continuous self-administration												

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				Off Therapy Evaluation[k]
Day		1[h]	8	15	22	1	8	15	22	1	8	15	22	
Informed consent	X													
NIH Advanced Directives Form[j]														
Demographics	X													
Medical history	X	X				X				X				
Concurrent meds	X	X----------X												
Physical exam	X	X				X				X				X
Vital signs	X	X	X[g]	X[g]	X[g]	X	X[g]	X[g]	X[g]	X	X[g]	X[g]	X[g]	X
Height	X													
Weight	X	X				X				X				
Performance status	X	X				X				X				X
CBC w/diff, plts	X					X				X				X
INR and PTT (or aPTT)	X													
Serum chemistry[b]	X	X				X				X				X
Urinalysis with dipstick[c]	X	X				X				X				
Urine protein-creatinine ratio (UPC)	X													
PSA	X	X				X				X				X
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Restaging radiologic evaluation[d]	X	Evaluations should be performed after every 3 cycles.												
Correlative studies [e]	X	X		X		X	X[i]	X[i]	X[i]	X				
Survival and post study														X[f]

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				Off Therapy Evaluation[k]
Day		1[h]	8	15	22	1	8	15	22	1	8	15	22	
anti-cancer therapy assessment														

a: AMG 386: Dose as assigned; administered I.V. every week without planned rest/break. One cycle = 28 days

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.

c: If the urine protein is ≥2+ a 24-hour urine collection for total protein should be obtained

d: CT chest, abdomen, pelvis; radionuclide bone scintigraphy; refer to section **11** for frequency of imaging studies

e: See section **9** for details as to pharmacodynamic/pharmacogenetic/pharmacokinetic timepoints/biomarkers to be drawn.

f: Will occur once every year until subject is off study or has died

g: Only subjects assigned to the AMG386 arm will have this assessment

h: Screening assessments may be used for Cycle 1 day as long as they are performed within the established screening timeframe indicated in section **3.2**.

i: Non AMG 386 patients will have these assessments on the 3 visits following cycle 2 day 1 (i.e. day 1 of cycle 3, 4 and 5)

j: As indicated in section **14.3**, all NIH Clinical Center subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

k: End of treatment visit will occur approximately 30 days after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms.

11 MEASUREMENT OF EFFECT

11.1 ANTITUMOR EFFECT – SOLID TUMORS

Re-staging bone scans and CT scan of chest, abdomen, and pelvis will be after every three cycles of treatment. If screening CT scan is negative for soft tissue disease, repeat CT imaging will not be required.

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. For exploratory purpose, changes in PSA and measurable lesions will be analyzed for efficacy according to the PCWG2 recommendations [JCO 26: 1148-1159, 2008]. The recommended PSA progressions criteria will not be applied to the study as the criteria are arbitrarily proposed and do not necessarily reflect overall disease status. PSA values will be captured at each visit and PSA declines and progression will be followed. PSA is not sufficient in the evaluation of disease progression in this patient population. This is consistent with the recent recommendations by the Prostate Cancer Clinical Trials Working Group 2. [*J Clin Oncol.* 26(7), 2008]. Progression will be determined by radiographic evidence as discussed below or by clinical symptoms (symptomatic clinical progression).

11.1.1 Definitions

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

Evaluable for objective response. All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) are evaluable for response. Patients that have: progressive disease, early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (not assessable, insufficient data) 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.

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

11.1.2 Disease Parameters

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

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

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.

11.1.3 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.

Metastatic bone lesions Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 3 or before cycle 4 (after the first staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required in the next scheduled staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 3, but no additional lesions are seen on confirmatory scans, the scans from after cycle 3 would serve as the baseline scan to evaluate for disease progression [*J Clin Onc*, 26 (7), 2008]

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:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

a. 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.

b. 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.

11.1.4 Response Criteria

11.1.4.1 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 of 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 of diameters while on study.

11.1.4.2 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).

11.1.4.3 Clinical Disease Progression

- Radiographic progression by CT scan or bone scan
- The need for palliative radiotherapy for pain
- The need for chemotherapy or other change in therapy based on increased cancer related symptoms
- Worsening ECOG PS to a PS of 3 or 4 based on cancer (not treatment) related symptoms

11.1.4.4 Evaluation of Best Overall Response

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

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

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

		No		
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

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease or death 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.

11.1.6 Progression-Free Survival

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

11.1.7 Radiographic Progression-Free Survival

Radiographic progression free survival (rPFS is defined as the duration of time from start of treatment to time of radiographic progression by CT scan (or MRI) or bone scan.

12 DATA COLLECTION / DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 DATA COLLECTION

Data will be collected prospectively and entered into NCI CCR C3D database. The NCI principal investigator is responsible for the collection, maintenance and quality control of study data.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g.: laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)
- Toxicity was assessed according to protocol (laboratory report slips, etc)
- Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts.. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security

standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

12.2 DATA REPORTING

12.2.1 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.

12.2.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center quarterly. The date for submission to the Coordinating Center 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 **12.2.1**).

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

12.3 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 E**.

- 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.

12.4 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) 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

The primary objective of the trial is to determine if there is a difference in progression free survival (PFS) among patients with metastatic prostate cancer without prior chemotherapy for metastatic castrate resistant disease who are randomized to receive either abiraterone/prednisone alone or in combination with AMG 386. PFS will be based on metastatic disease (measurable or non-measurable but not PSA), using clinical and radiographic criteria.

The study will be conducted with a two-part design. In the initial run-in part of the trial, the study will evaluate patients in two cohorts of escalating dose levels from 15mg/kg to 30mg/kg. Based on a standard 3 to 6 per cohort dose escalation, the first 3 patients would be treated at a 15mg/kg dose, and then the next cohort of 3 patients will be treated at 30mg/kg provided there are 0 of 3 patients with unacceptable toxicity at the 15mg/kg dose. If 1 of 3 patients has a dose limiting toxicity at 15mg/kg, then 3 more patients will be enrolled at that dose. If 1 of 6 has unacceptable toxicity, then accrual would escalate to the 30mg/kg dose. If 1 of 3 patients has dose limiting toxicity at 30mg/kg, then 3 more patients will be enrolled at that dose. Three to 6 patients will be tested at the 30mg/kg dose. The dose selected for evaluation will be determined after review by the sponsor (CTEP and the study team). The maximum dose at with 6 patients are treated and no more than 1/6 has dose limiting toxicity will strongly factor into this decision.

In the second part of the trial, patients without prior chemotherapy for metastatic castrate resistant disease will be enrolled at the AMG 386 dose level of 30 mg/kg, established in the run in phase as of Amendment F.

In patients who have not received chemotherapy for metastatic castrate resistant disease based on preliminary results reported from ASCO in 2012, patients with this disease but treated with abiraterone/prednisone alone would be expected to have an estimated, approximate10 month median progression free survival from the date of randomization, using both clinical and radiologic determinants of progression. This is based on the published results showing what may become a median 12 month PFS by radiologic criteria alone, and allowing for earlier progression by clinical determinations. The goal of this study will be to determine if the use of AMG 386 in addition to abiraterone/prednisone will result in an 8 month increase in median progression free survival from randomization, to a median of 18 months. Kaplan-Meier curves and a one-tailed log-rank test will be the primary analysis methods. Assuming exponential progression free survival curves, the hazard rate for the abiraterone/prednisone alone arm will be 0.0693, or approximately a 6.9% probability of progression each month when the median progression free survival is 10 months. If we assume that the combination arm has a median progression free survival of 18 months, this corresponds to a hazard rate of 0.0385 and the resulting hazard ratio for the comparison of the two overall progression free survival curves would be 1.80. To compare these curves and detect a difference with a 0.10 one-tailed log-rank test, following a phase 2.5 design, a total of 36 evaluable subjects per arm (72 total) will need to be enrolled

without prior chemotherapy for metastatic castrate resistant disease in the part 2 portion of the study over a three year period and followed for an additional year from the date of entry of the last patient, with observation of 52 total progressions, in order to have 80% power to compare the curves. In order to allow for early termination of the randomized portion of the trial in the event that the AMG 386 arm is not associated with improvement in PFS, the following stopping rule will be implemented: if after 50% of the information has been observed (26 events), the observed hazard ratio (AMG/non-AMG) exceeds 1.0, no further patients will be enrolled.

In addition, for each randomized arm of the trial, an early stopping rule for evidence of unacceptable toxicity will be implemented. If after 18 patients have been treated on a given arm, if 6 patients experience a DLT, then no further patients will be enrolled on the trial. For a given arm, 5 of 18 with a DLT has an upper one-sided 90% confidence interval of 45.5% while 6 of 18 has an upper one-sided 90% confidence interval of 51.2%. Thus, 5 of 18 with toxicity is likely to be inconsistent with 50% having severe toxicity while 6 of 18 would potentially be consistent with 50% or greater having severe toxicity.

Patients will be stratified according to prior ketoconazole or enzalutamide use versus no prior ketoconazole or enzalutamide use. At the conclusion of the trial, patients will be evaluated for outcome (response, OS, PFS) according to prior use of ketoconazole or enzalutamide, but as a secondary evaluation and without formal adjustment for multiple comparisons.

13.2 Sample Size/Accrual Rate

It is anticipated that this trial may enroll approximately 3 patients per month; thus accrual is expected to be completed within 2-3 years for both the phase I and randomized phase II portions. Up to 12 patients may be required for the run-in part plus 72 without prior chemotherapy for metastatic castrate resistant disease in the randomized part. In order to allow for the possibility that there may be a very small number of patients who are inevaluable, the accrual ceiling will be set at 88 patients.

The accrual rate is expected to be rapid since there will be a desire for patients to receive abiraterone, which will be supplied by the clinical center. Also, there is a local GU consortium that could assist in accrual by sending patients to the clinical center.

13.3 Stratification Factors

Randomization will be stratified according to prior ketoconazole use or enzalutamide use versus no prior ketoconazole or enzalutamide use.

13.4 Analysis of Secondary Endpoints

Overall survival will also be evaluated using Kaplan-Meier curves, and a one-tailed log rank test, as a secondary endpoint.

Evaluation of circulating tumor cells will also be performed as an exploratory analysis, comparing values between arms relative to changes from baseline. Angiogenic and genetic biomarkers will also be explored in relation to evaluating the impact of treatments on outcome.

Monthly PSA, testosterone, CBC, and serum chemistries will be performed at baseline and monthly thereafter, with CT scans and bone scans to be performed at baseline and every 8 weeks of treatment until progression. The comparisons will be made without any correction for multiple comparisons because of the exploratory and secondary nature of the evaluations.

Toxicity of the agent will also be tabulated for all patients taken as a group, and potentially by type of polymorphism genotype expression in the event that this may have some association. The distributions of toxicity identified will be compared informally to data from the same agent in other trials.

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 and/or abiraterone

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). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should 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. Precise definitions for categories 4-9 will be protocol specific.

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

13.5.3 Evaluation of DLT For MTD determination, dose-limiting toxicities will be evaluated throughout the first 28 days of treatment.

14 Human Subjects Protections

14.1 Rationale For Subject Selection

Subjects treated on this study, will be individuals with metastatic progressive, castrate-resistant prostate cancer with radiographic evidence of disease after primary treatment with surgery or radiotherapy which has continued to progress despite adequate androgen-deprivation therapy.

Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

14.1.1 NCI IRB Multi-Institutional Guidelines

14.1.1.1 IRB Approvals

The PI will provide the NCI IRB and Central Registration Office with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

14.1.1.2 Amendments and Consents

The CCR PI will provide the NCI IRB with copies of all amendments, consents and approvals from each participating institution.

14.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have prostate cancer, and because of unknown toxicities in the pediatric population.

14.3 PARTICIPATION OF **NIH** SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **14.5**), all NIH Clinical Center subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Subjects participating in this protocol may potentially benefit from an improvement in metastatic lesions, reduction in tumor bulk, which may or may not favorably impact symptoms and survival. Potential risks include the range of side effects listed in section **7.1.1**. Subjects will be evaluated medically throughout the protocol in order to minimize risk.

14.5 RISKS/BENEFITS ANALYSIS

For patients with castration resistant prostate cancer, median survival is in the range of 12-18 months. The agents administered in this trial have shown activity against prostate cancer in vitro and in vivo. Although possible toxicities from the proposed therapy are serious, given the nature of the underlying disease, they are reasonable. Additionally, we do not anticipate toxicities

significantly more severe than those observed with other, approved agents. For these reasons, the risk/benefit ratio of this protocol is favorable; therefore, this protocol involves greater than minimal risk to patients, but presents the potential for direct benefit to individual subjects.

14.6 CONSENT PROCESS AND DOCUMENTATION

Patients will meet with an associate or principal investigator on the trial in the Prostate Cancer Clinic, during the initial evaluation for this study. During that meeting, the investigator will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility. The original signed consent goes to Medical Records; copy placed in research record (NIH policy).

If re-consent is required, an informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

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

14.6.1 Informed Consent of Non-English Speaking Subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of

the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

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16 APPENDICES

16.1 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.

16.2 APPENDIX B: DOSE CALCULATION TABLES FOR AFTER DEPLETION OF 240 MG SUPPLY

Table 3: 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

Table 4: Dose Level 30 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	900	2	1	3
35 to 44.9	1200	0	2	2
45 to 54.9	1500	2	2	4
55 to 64.9	1800	0	3	3
65 to 74.9	2100	2	3	5
75 to 84.9	2400	0	4	4
85 to 94.9	2700	2	4	6
95 to 104.9	3000	0	5	5
105 to 114.9	3300	2	5	7
115 to 124.9	3600	0	6	6
125 to 134.9	3900	2	6	8
135 to 144.9	4200	0	7	7
145 to 154.9	4500	2	7	9
155 to 164.9	4800	0	8	8
165 to 174.9	5100	2	8	10
175 to 184.9	5400	0	9	9
185 to 194.9	5700	2	9	11
195 to 204.9	6000	0	10	10

Table 5: Dose Level 10 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	300	2	0	2
35 to 44.9	400	0	1	1
45 to 54.9	500	0	1	1
55 to 64.9	600	0	1	1
65 to 74.9	700	1	1	2
75 to 84.9	800	2	1	3
85 to 94.9	900	2	1	3
95 to 104.9	1000	3	1	4
105 to 114.9	1100	0	2	2
115 to 124.9	1200	0	2	2
125 to 134.9	1300	1	2	3
135 to 144.9	1400	2	2	4
145 to 154.9	1500	2	2	4
155 to 164.9	1600	3	2	5
165 to 174.9	1700	0	3	3
175 to 184.9	1800	0	3	3
185 to 194.9	1900	1	3	4
195 to 204.9	2000	2	3	5

16.3 APPENDIX C: LIST OF DRUGS THAT MAY HAVE POTENTIAL CYP2D6 INTERACTIONS

CYP2D6 Substrates

Amitriptyline	Doxepin	Methylphenidate	Propranolol
Amoxapine	Doxorubicin	Metoprolol	Protriptyline
Aripiprazole	Duloxetine	Mexiletine	Risperidone
Atomoxetine	Flecainide	Mirtazapine	Sertraline
Betaxolol	Fluoxetine	Moclobemide	Tamoxifen
Captopril	Fluphenazine	Nefazodone	Tamsulosin
Carvedilol	Fluvoxamine	Nortriptyline	Thioridazine
Chloroquine	Haloperidol	Oxycodone	Timolol
Chlorpromazine	Hydrocodone	Paroxetine	Tolterodine
Clomipramine	Imipramine	Perphenazine	Tramadol
Codeine	Labetalol	Pindolol	Trimipramine
Desipramine	Lidocaine	Pipotiazine	Venlafaxine
Dextroamphetamine	Lomustine	Procainamide	Zuclopenthixol
Dextromethorphan	Maprotiline	Promethazine	
Dihydrocodeine	Methamphetamine	Propafenone	

CYP2D6 Inhibitors

Acebutolol	Dolasetron	Metoclopramide	Quinine
Amiodarone	Doxorubicin	Metoprolol	Rabeprazole
Amitriptyline	Duloxetine	Miconazole	Ranitidine
Amlodipine	Entacapone	Mifepristone	Risperidone
Amphetamine	Escitalopram	Moclobemide	Ritonavir
Azelastine	Felodipine	Nefazodone	Ropinirole
Bepridil	Fexofenadine	Nelfinavir	Rosiglitazone
Betaxolol	Flecainide	Nevirapine	Saquinavir
Biperiden	Fluoxetine	Nicardipine	Selegiline
Bortezomib	Fluphenazine	Nifedipine	Sertraline
Buprenorphine	Fluvastatin	Nortriptyline	Sildenafil
Bupropion	Fluvoxamine	Olanzapine	Simvastatin
Celecoxib	Gefitinib	Omeprazole	Sulconazole
Chloroquine	Halofantrine	Ondansetron	Telithromycin
Chlorpheniramine	Haloperidol	Orphenadrine	Terbinafine
Chlorpromazine	Hydroxyzine	Oxprenolol	Thioridazine
Cholecalciferol/Vitamin D_3	Imatinib	Oxybutynin	Thiothixene

Cimetidine	Imipramine	Paroxetine	Ticlopidine
Cinacalcet	Indinavir	Pentamidine	Timolol
Cisapride	Irbesartan	Pergolide	Tioconazole
Citalopram	Isoniazid	Perphenazine	Tranylcypromine
Clemastine	Ketoconazole	Pimozide	Trazodone
Clomipramine	Labetalol	Pindolol	Tripelennamine
Clotrimazole	Lansoprazole	Pioglitazone	Triprolidine
Clozapine	Lidocaine	Pravastatin	Valproic acid
Cocaine	Lomustine	Praziquantel	Venlafaxine
Codeine	Loratadine	Primaquine	Verapamil
Delavirdine	Lovastatin	Promethazine	Vinblastine
Desipramine	Mefloquine	Propafenone	Vinorelbine
Dexmedetomidine	Methadone	Propofol	Yohimbine
Dextromethorphan	Methimazole	Propoxyphene	Zafirlukast
Diltiazem	Methotrimeprazine	Propanolol	Ziprasidone
Diphenhydramine	Methoxsalen	Pyrimethamine	
Disulfiram	Methylphenidate	Quinidine	

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

There are no known CYP2D6 inducers. Only major substrates are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

Updated on May 1, 2007

16.4 APPENDIX D: NCI IRB **PROBLEM FORM**

<table>
<tr><td>NCI Protocol #:</td><td>Protocol Title:</td></tr>
<tr><td></td><td>Report version: (select one)
____Initial Report
____Revised Report
____Follow-up</td></tr>
<tr><td>Site Principal Investigator:</td><td></td></tr>
<tr><td>Date of problem:</td><td>Location of problem: (e.g., patient's home, doctor's office)</td></tr>
<tr><td colspan="2">Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc…)</td></tr>
<tr><td>Brief Description of Subject (if applicable)
(Do NOT include personal identifiers)</td><td>Sex: ___ Male ___ Female Age:
___ Not applicable (more than subject is involved)</td></tr>
<tr><td colspan="2">Diagnosis under study:</td></tr>
<tr><td colspan="2">Name the problem: (select all that apply)
[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis
[ ] Sepsis/Infection
[ ] Blood product reaction</td></tr>
</table>

[ ] Unanticipated surgery/procedure

[ ] Change in status (e.g. increased level of care required)

[ ] Allergy (non-medication)

[ ] Fall

[ ] Injury/Accident (not fall)

[ ] Specimen collection issue

[ ] Informed consent issue

[ ] Ineligible for enrollment

[ ] Breach of PII

[ ] Tests/procedures not performed on schedule

[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):

***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO
Please explain:

***Is this problem related or possibly related to participation in the research?** __YES __NO
Please explain:

***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**

Is this problem? (*select all that apply*)

[ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious

[ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious

[ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO **If "Yes", how many? ____ Please describe:**
Describe what steps you have already taken as a result of this problem:
In addition to the NCI IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**

Adverse Event Information:

CTCAE Term	**Date of Event**	**Location of Event**	**CTCAE Version**	**CTCAE Grade**	**Attribution to Research**	**Attribution to IND Agent**	**Expected**
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No
	Click here for date.	Location of Event	Version No	Grade No	Attribution	Attribution	Yes/No

REPORTED BY:

Printed Name

Date

16.5 APPENDIX E: 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.

INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0079 PRINCIPAL INVESTIGATOR: Ravi Madan, M.D.

STUDY TITLE: A Phase II Multicenter Study of AMG 386 and Abiraterone in Metastatic Castration Resistant Prostate Cancer

Continuing Review Approved by the IRB on 07/25/16

Amendment Approved by the IRB on 01/18/17 (R) Date Posted to Web: 01/28/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Prostate cancer is the most common cancer among American men and the second leading cause of cancer related death. The majority of these deaths occur among men with metastatic disease (disease that has spread to distant locations in the body). Because androgens (male hormones) stimulate prostate cancer cells to grow, and because lowering androgen levels often leads to slower growth in prostate cancer, androgen-deprivation therapy (reducing the level of androgens in the body) is the mainstay of treatment for metastatic prostate cancer. However, nearly all men with metastatic prostate cancer eventually become resistant to androgen deprivation and experience progression of their disease. These types of cancers are referred to as castration-

resistant. Once castration-resistant prostate cancer develops, most patients do not live more than 18 – 24 months.

It has been shown that interfering with the formation of blood vessels that feed the tumor can reduce tumor growth in prostate cancer cells. AMG 386 is an investigational or experimental anticancer agent that targets the blood vessels that feed the tumor. It has not been approved by the Food and Drug Administration for use in prostate cancer. AMG 386 has to date been used in a total of 1190 subjects in clinical trials of the agent for a variety of tumor types. None however was focused on prostate cancer. Side effects occurring during these trials are listed in the risks and side effects section below. The purpose of this study is to first establish a safe dose of AMG 386 to be used in the study and then to determine whether adding this dose of AMG 386 to an androgen deprivation regimen of abiraterone and prednisone in men with castration-resistant prostate cancer improves the amount of time it takes for the disease to progress.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have been diagnosed with metastatic (distantly spread) prostate cancer that does not respond to therapy designed to lower the androgen levels in your body.

How many people will take part in this study?

88 subjects will be enrolled in this study at the NIH Clinical Center and at other centers in the United States. Of these, a maximum of 12 subjects will be enrolled to the first stage of the study for determining the appropriate dose of AMG 386.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to the study team.

These tests include:

- A complete medical history will be taken from you, a history of your cancer, and prior cancer treatments you have taken.
- You will be asked to give information about all drugs (including over the counter drugs, vitamins and herbal supplements) that you are currently taking.
- Your doctor will do a complete physical examination; assess your ability to do physical activities, measure your blood pressure, heart rate, and respiration rate.

- You will be asked to have a 12-lead electrocardiogram (ECG) and a chest x-ray
- A sample of your blood (approximately 2 tablespoon) will be taken for laboratory testing including PSA measurements.
- A urine sample for measurement of protein in the urine.
- An evaluation of your cancer will be done. This will include a CT scan and bone scan.

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- PSA measurements
- Blood tests including blood counts and chemistries

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study. If these tests were done at screening, they will not be repeated for day 1 of cycle 1.

- Bone scan and CT scan of the chest, abdomen, and pelvis after every 3 cycles
- Vital signs - every week in lead in and group 1 patients, day 1 (+/- 5 days) of each cycle for group 2 patients
- History and physical examination - day 1 (+/- 5 days) of each cycle
- Blood tests to evaluate toxicities- every 4 weeks

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body. (Blood may be collected within +/- 5 days of what is indicated below)

- 10 mL (~ 2 teaspoons) of blood collected once after you have enrolled but before you have received any study drug
- 5 mL (~ 1 teaspoon) blood collected before you receive the study drug on the following days: day 1 of cycle 1, day 15 of cycle 1, day 1 of cycle 2 and day 1 of cycle 3
- 10 mL (~ 2 teaspoons) of blood at the following times: days 1 and 15 of cycle 1 before you have received the study drug
- 14 mL (~2.8 teaspoons) of blood at the following times: days 1 and 15 of cycle 1 before you have received the study drug
- 6 mL (~ 1.2 teaspoons) of blood collected on the following times: cycle 2 day 1 and the next 3 visits

This study will be conducted on an outpatient basis in two stages.

In stage 1, or the lead-in phase, a maximum of 12 subjects (up to 6 at each dose) will be assigned to take either a 15 mg/kg dose or, if there are no serious side-effects at 15 mg/kg, a 30 mg/kg dose of AMG 386. Subjects will receive the assigned dose through an IV catheter (a plastic tube in your vein) once per week for a total of 4 doses during a 28-day cycle. Subjects will also take 1000 mg of abiraterone once a day by mouth and depending on your preference, either 5 mg twice per day or 10 mg once per day of prednisone by mouth on each day of the cycle. If 2 or more subjects experiences serious side-effects at the 15 mg/kg dose the study will end. If no more than 1 person experiences serious side-effects, another group of up to 6 subjects will be enrolled to take a dose of 30 mg/kg of AMG 386. If 2 or more subjects experience serious side-effects, the dose for stage 2 of the study will be established at 15 mg/kg. If no more than 1 person experiences serious side-effects at the 30 mg/kg dose, the dose for stage 2 of the study will be established at 30 mg/kg. Unless you experience serious side-effects or your disease progresses, there is no limit to the number of cycles you may remain on the study regimen. Therapy may be stopped, however, for any of the reasons listed in the stopping therapy section below.

If you are enrolled for stage 2 of the study, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1 (often called "Arm A"), you will be assigned to take a 1000 mg of abiraterone once a day by mouth and depending on your preference either 5 mg twice per day or 10 mg once per day of prednisone by mouth on each day of the 4 week cycle. You will be evaluated for serious side-effects and your response to therapy on the schedule described above. Unless you experience serious side-effects or your disease progresses, there is no limit to the number of cycles you may remain on the study regimen. Therapy will be stopped, however, for any of the reasons listed in the stopping therapy section below.

If you are in group 2 (often called "Arm B"), you will be assigned to take a weekly dose of AMG 386 that was established in stage 1 by IV along with 1000 mg of abiraterone once a day by mouth and depending on your preference, either 5 mg twice per day or 10 mg once per day of prednisone by mouth on each day of the 4 week cycle. The AMG 386 dose for stage 2 of the study was established at 30 mg/kg.
You will be evaluated for serious side-effects and your response to therapy on the schedule described above. Unless you experience serious side-effects or your disease progresses, there is no limit to the number of cycles you may remain on the study

regimen. Therapy will be stopped, however, for any of the reasons listed in the stopping therapy section below.

You should take abiraterone in the morning. However, if that dose is missed, you should make up the dose during the remainder of the day. Do not take two doses of abiraterone on the same day. Do not have any food for at least 2 hours before and 1 hour after taking the abiraterone.

You should take prednisone at around the same time every day with the doses approximately 12 hours apart, give or take two hours if you are taking prednisone twice per day or approximately 24 hours apart give or take two hours if you are taking prednisone once per day. Prednisone should, if possible, be taken with food or milk to reduce stomach irritation. If you miss a dose of prednisone, that is, if more than 14 hours (or 36 hours in case of once a day dosing) have passed since the previous dose, you should not make up that dose. Instead, you should resume taking the drug at the next scheduled dose.

We ask that you avoid eating or drinking grapefruit and grapefruit products including grapefruit juice while enrolled on study as this may adversely interact with one of the study drugs (abiraterone).

When you are finished receiving the drugs (treatment):

Your participation in this study will continue until either you or your study team decides that this medication is not beneficial to you. Your participation is voluntary; so you may stop receiving the study drugs at any time, but we ask that you speak to your study team before stopping. Your study team will be monitoring you and your cancer while you are receiving the study treatment. If your prostate cancer is clearly worsening, then your study team will stop treatment with the study drugs. At the end of the study, no additional testing will be required outside of the routine blood work for regular cancer care. If you stop the drug because of side effects, the study team may request that you continue follow-up and/or testing for this until resolution. In addition, we will contact you and or your primary care physician by telephone once per year to determine your survival status.

Study Chart

A cycle in this study = 28 days. The cycle will be repeated until any of the stopping therapy criteria are met. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle (+/- 5 days) and the right-hand column tells you what to do on that day.

Cycle 1

Within 4 weeks before study enrollment	• CT scan and bone scan
Within 16 days before enrollment	• Routine blood tests and urinalysis
Within 1 week before enrollment	• PSA, medical history and physical exam
At enrollment (stage 2 only)	• Get randomized to take AMG 386 along with abiraterone and prednisone or to take abiraterone and prednisone alone
After enrollment but before starting study regimen	• ~1 - 2 teaspoons of blood drawn for research tests
Day 1	Prior to taking AMG 386 • ~7 teaspoons of blood drawn for research tests • History and physical exam • Vital signs • Urinalysis • Routine blood tests Study drugs • Begin receiving AMG 386 by IV once per week (lead in and group 1 only) • Begin taking abiraterone once a day • Begin taking prednisone twice per day *Keep taking the medications until you are told to stop by your health care team.*
Day 8	• Vital signs (lead in and group 1 patients only)
Day 15	• Get vital signs taken (lead in and group 1 patients only) • ~6 teaspoons blood drawn for research tests
Day 22	• Vital signs (lead in and group 1 patients only)

Future cycles

Days 1-28	Study drugs • Continue receiving AMG 386 by IV once per week. (lead in and group 1 patients only) • Keep taking abiraterone once a day • Keep taking prednisone twice per day Routine assessments • Vital signs– days 1 for all patients and also days 8, 15 & 22 of each cycle for patients lead in and group 1 patients • History and physical exam (including weight) – day 1 of each cycle • Urinalysis and routine blood tests – day 1 of each cycle • Bone scan and CT-scan – day 1 after every 3 cycles Research blood tests • ~ 1 teaspoon of blood drawn for research tests on day 1 of cycle 2 and day 1 of cycle 3 • ~1.2 teaspoon of blood drawn for research tests on cycle 2 day 1 and the next 3 visits

Birth Control

Because the effects of AMG 386 on the developing human fetus are unknown, men participating in this study must agree to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you think that your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

You should recognize that no method of birth control besides abstinence provides 100% protection from pregnancy.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Risks and side effects in this study are mainly due to the side effects of the study agents:

AMG 386

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The AMG 386 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Table of Possible Side Effects for AMG 386

COMMON, SOME MAY BE SERIOUS In 100 people receiving AMG 386, more than 20 and up to 100 may have:
• Pain • Diarrhea, nausea, vomiting • Swelling of the body • Tiredness • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Loss of appetite • High blood pressure which may cause headaches, dizziness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving AMG 386, from 4 to 20 may have:
• Heart attack • Blurred vision • Blood clot which may cause blindness, swelling, pain, or shortness of breath • Fluid in the body • Damage to the lungs which may cause shortness of breath • Bleeding

Abiraterone

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Abiraterone Acetate, more than 20 and up to 100 may have:
• Swelling of the body

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Abiraterone Acetate, from 4 to 20 may have:

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Abiraterone Acetate, from 4 to 20 may have:
• Heartburn, diarrhea • High blood pressure which may cause headaches, dizziness, blurred vision • Flushing

RARE, AND SERIOUS In 100 people receiving Abiraterone Acetate, 3 or fewer may have:
• None

Prednisone

(Table Version Date: June 24, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Increased appetite and weight gain • Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Glaucoma • Infection • Non-healing wound • Diabetes • Damage to the bone which may cause joint pain and loss of motion • Kidney stones • Heartburn

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will prolong the time that it takes for your disease to progress. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- The study agents, AMG 386, abiraterone and prednisone will be provided by the NIH Clinical Center pharmacy. In some cases, the NIH Clinical Center may not supply abiraterone or prednisone but it can also be obtained from a local site pharmacy. You or your insurance company may have to pay for medications that are not provided at the NIH Clinical Center. You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:
- if he/she believes that it is in your best interest
- if your disease progresses during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Amgen or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Amgen or any subsequent pharmaceutical collaborator
- National Cancer Institute Institutional Review Board
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug, AMG 386, developed by Amgen through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi A. Madan, M.D., Building 10, Room 13N240B, Telephone: 301-480-7168. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 25, 2016 THROUGH JULY 24, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____