A Phase II study of bevacizumab in combination with ixabepilone in subjects with advanced renal cell carcinoma

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PRÉCIS

Background:
- Substantial preclinical antitumor synergy supports the exploration of the combination of antiangiogenic compounds (including sunitinib and bevacizumab) plus ixabepilone. *In vivo*, synergistic activity between ixabepilone and bevacizumab has been demonstrated using the 151-B human renal carcinoma xenograft model and this synergy compares favorably with other antiangiogenic inhibitors (i.e. sunitinib).
- Combination therapies of bevacizumab with chemotherapy demonstrated improved benefit compared with single-agent cytotoxics in multiple animal models and in humans.
- Clinical activity of both compounds used as single agents has been demonstrated in a broad spectrum of solid tumors. Bevacizumab and ixabepilone, when used as a single agent, have demonstrated substantial activity in renal cell carcinoma.
- Phase II studies with bevacizumab and ixabepilone suggest the absence of overlapping toxicities.
- Development of a well-tolerated and active bevacizumab/ixabepilone combination has the potential to further improve the treatment of metastatic renal cell carcinoma (mRCC), and could represent a second-line option after sunitinib or sorafenib are no longer of benefit or are intolerable.

Primary Objective
- Determine the objective response rate of the combination of ixabepilone and bevacizumab in patients with relapsed or refractory mRCC.
- Determine progression-free survival.
- Characterize the toxicity of the combination of ixabepilone and bevacizumab in patients with mRCC.
- Determine changes in biomarkers and evaluate correlation with clinical outcomes.
- Assess the toxicity profile of the combination of ixabepilone and bevacizumab in patients with relapsed or refractory mRCC.

Eligibility
- Presence of metastatic renal carcinoma, after progression or intolerance to VEGFR inhibitors (sunitinib and/or sorafenib).
- Adequate organ and bone marrow function.

Design
- Single-center, open labeled phase II study
- Following a Simon two-stage optimal design, a maximum of 58 patients with metastatic RCC will be accrued over a period of 24 months.
- Ixabepilone will be administered daily as a one hour infusion on five successive days (daily x 5), every three weeks (one cycle equals 3 weeks or 21 days). The starting dose will be a daily dose of 6 mg/m²/day, for a total per cycle dose of 30 mg/m².
- In addition, 15 mg/kg bevacizumab will be administered intravenously on day 1 of each cycle. The first infusion of bevacizumab will be 90 minutes in duration, the second 60 minutes in duration, and in all subsequent cycles bevacizumab will be infused over 30 minutes if prior infusions are well tolerated.
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1. INTRODUCTION

1.1 OBJECTIVES

Primary Objective
- Determine the objective response rate using RECIST criteria of the combination of ixabepilone and bevacizumab in patients with relapsed or refractory metastatic renal cell carcinoma (mRCC).

Secondary Objectives
- Determine progression-free survival.
- Characterize the toxicity of the combination of ixabepilone and bevacizumab in patients with mRCC.
- Determine changes in biomarkers (tissue tumor biopsy and blood-based proteins, circulating endothelial cells, tumor endothelial markers) and evaluate correlation with clinical outcomes. Analysis will include microvessel density and protein determination involved in the angiogenic pathway.
- Assess the toxicity profile of the combination of ixabepilone and bevacizumab in patients with relapsed or refractory mRCC.

1.2. BACKGROUND

1.2.1 BEVACIZUMAB

Background:
Bevacizumab (rhuMAb) is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigen-binding complementarity-determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1) which blocks the binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human IgG1, and ~7% of the sequence is derived from the murine antibody [1].

Preclinical data:
In cynomolgus monkeys, twice weekly IV treatments with bevacizumab (doses of 2, 10 and 50 mg/kg) for 4, 13 or 26 weeks were well tolerated, with no overt signs of acute toxicity [2]. Animals with open growth plates showed physeal dysplasia as well as focal to diffuse chondroid necrosis and linear fissuring of the cartilaginous growth plate. Females treated with 10 - 50 mg/kg twice weekly had decreased ovarian and uterine weights, which were associated with absence of corpora lutea. These findings were expected, considering the known role of VEGF in formation of the corpora lutea and of the growing bone [3]. In a further study physeal dysplasia and ovarian and uterine changes induced by rhuMAb VEGF were partially reversible using a similar treatment regimen in the recovery period. No antibodies against bevacizumab were detected.

Phase I Clinical studies:
Two phase I studies have been performed. Study AVF0737g was a dose escalation trial of single and multiple intravenous (IV) administration of rhuMAb in patients with advanced malignancies. Five dose levels were evaluated (0.1, 0.3, 1.0, 3.0, and 10 mg/kg). rhuMAb VEGF was administered as a 90-minute infusion on days 0, 28, 35 and 42 [4]. The second study, AVF0761g, evaluated multiple doses of rhuMAb VEGF 3 mg/kg weekly for up to 8 weeks in combination with one of three cytotoxic chemotherapy regimens (5-fluorouracil/leucovorin, carboplatin/paclitaxel, or doxorubicin).
in subjects with advanced solid malignancies [5]. rhuMAb VEGF was administered weekly at 3 mg/kg for eight doses.

In both studies, rhuMAb VEGF appeared to be well tolerated. In AVF0737g, 3 of 25 patients treated experienced tumor-related hemorrhagic events, possibly related to the administration of rhuMAb VEGF. In two cases the event was considered serious: an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and bleeding at the tumor site in a 38-year-old woman with a slowly progressing sarcoma of the thigh. No patient in AVF0761g reported serious bleeding. No dose limiting toxicity was reached in either study. No antibodies to rhuMAb VEGF were detected after therapy in either study.

**Pharmacokinetics:**
In study AVF0737g, the pharmacokinetics of rhuMAb VEGF appeared to be linear for doses \( \geq 1 \text{mg/kg} \) with a half-life of approximately 15 - 21 days. Comparable pharmacokinetic data was seen in study AVF0761g. Co-administration of rhuMAb and cytotoxic chemotherapy did not appear to result in a change in the systemic concentration of the cytotoxic agents.

**Phase II Clinical Studies:**
Bevacizumab has been shown to be effective in the therapy of metastatic renal cell carcinoma. Yang et al. [6] completed a randomized, double-blind, phase 2 trial comparing placebo to bevacizumab at doses of 3 and 10 mg/kg given every 2 weeks. There was a statistically significant increase in time to progression with the high-dose group compared to placebo.

**Phase III studies:**
In a recent phase III study, the addition of bevacizumab to conventional chemotherapy (paclitaxel plus carboplatin) in the treatment of selected patients with advanced **non-small cell lung cancer** resulted in a significant survival benefit [8]. Rates of clinically significant bleeding were 4.4% (bevacizumab arm) vs. 0.7% (control arm; \( p < 0.001 \)). There were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including 5 from pulmonary hemorrhage.

More recently, the activity of bevacizumab was demonstrated in metastatic **breast carcinoma (MBC)**. A phase III trial [9] of bevacizumab (15 mg/kg every 3 weeks) plus capecitabine (2500 mg/m\(^2\) daily) in patients with heavily pretreated MBC reported a significantly increased overall response rate compared with capecitabine alone, as determined by an independent review panel (19.8% (95% confidence interval (CI): 14.7–25.0) versus 9.1% (95% CI: 5.4–12.9), respectively; \( P = 0.001 \)). However, there was no difference between the two treatment arms in terms of progression-free survival (PFS).
(the primary endpoint of the study; median 4.86 months in the capecitabine plus bevacizumab arm versus 4.17 months in the capecitabine alone arm; hazard ratio (HR) = 0.98 (95% CI: 0.77–1.25)) or overall survival (OS) (median 15.1 months versus 14.5 months, respectively). A further phase III trial evaluated weekly paclitaxel with or without bevacizumab (10 mg/kg every 2 weeks) in patients with previously untreated locally recurrent or MBC [10]. The trial was stopped early, at the first scheduled interim analysis, on the recommendation of the independent Data Monitoring Committee, which concluded that the trial had already met its primary efficacy endpoint. Since these interim data were released, a number of data sets have been presented that differ according to data cut-off dates and study population definitions. Data used to support the regulatory submission to the Food and Drug Administration (FDA) were based on the same cut-off date as the interim analysis and these are presented below. Median PFS was approximately doubled, from 5.8 months for patients receiving paclitaxel alone to 11.4 months for patients receiving paclitaxel plus bevacizumab (P < 0.0001) [11]. In addition, the overall response rate was more than doubled, increasing from 23.4% for paclitaxel alone to 48.0% for paclitaxel plus bevacizumab (P < 0.0001). At the time of the interim analysis, there was a trend towards increased OS for patients receiving bevacizumab in combination with paclitaxel (26.5 months versus 24.8 months), although the increase was not statistically significant compared with patients receiving paclitaxel alone (HR = 0.87; 95% CI: 0.72–1.05). However, at 1 year, survival in the combination arm was significantly better than in the paclitaxel alone arm (81.4% versus 74.0%; P = 0.017). Of note, the censoring rate after 12 months follow-up is >10%, which precludes any valid conclusion on OS. In addition, the impact of subsequent treatment after disease progression on OS remains unclear, particularly for patients in the paclitaxel alone arm. The magnitude of the observed PFS benefit in this trial is one of the largest seen when compared with other randomized trials that have led to the registration of chemotherapy regimens for first-line MBC treatment. Based on these data, the European Medicines Agency (EMA) and FDA have approved bevacizumab in combination with paclitaxel for the first-line treatment of patients with MBC.

The most recent report to be added in metastatic renal cell carcinoma (mRCC) is that of Escudier and colleagues, who randomized patients between bevacizumab plus interferon and interferon alone. This trial was conducted in first-line treatment for mRCC. This study demonstrated improved progression free survival from 5.4 months to 10.2 months with the addition of bevacizumab; data for overall survival have not yet been reported [12].

Additional clinical trials are ongoing in a variety of solid tumors and hematological malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biological agents.

1.2.2 IXABEPILON (BMS-247550).

Ixabepilone (BMS-247550) is a member of the novel class of non-taxane microtubule stabilizing compounds known as epothilones. The epothilones are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of the cellulose degrading myxobacteria, Sorangium cellulosum [17]. Similar to paclitaxel and other taxanes, epothilones block cells in mitosis, resulting in cell death [18]. Ixabepilone has been developed by Bristol-Myers Squibb for use in the treatment of cancer.

Preclinical pharmacology studies [19, 20].

Ixabepilone has demonstrated significant improvement over paclitaxel in several critical aspects. Ixabepilone is active against cancer models that are naturally insensitive to paclitaxel or have developed resistance to paclitaxel, both in-vitro and in-vivo.
Ixabepilone exhibits a very impressive and broad spectrum of antitumor activity against paclitaxel-sensitive (A-2780, HCT 116 and LS 174T) tumors as well as paclitaxel-resistant human colon tumors (HCT116/VM46), ovarian carcinoma (Pat-7 and A2780Tax) and breast carcinoma (Pat-21) models. Ixabepilone is orally efficacious; the antitumor activity produced after oral administration is comparable to that produced by parenteral administration of the drug. Synergistic activity of Ixabepilone with a number of antineoplastic agents has been demonstrated in vitro [20]. These preclinical efficacy data suggest that ixabepilone has the potential to demonstrate improved clinical efficacy in paclitaxel-insensitive and sensitive disease types.

Chemistry [19].

The epothilones are a new class of agents that like the taxanes, promote the polymerization of tubulin. The epothilones are obtained from the fermentation of the myxobacterium, Sorangium cellulosum. The chief components of the fermentation process are epothilones A and B. These natural products are polyketide derived, sixteen-membered ring macrolides. BMS–247550, [1S-[1R*, 3R*(E), 7R*, 10S*, 12R*, 16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione, is a semisynthetic derivative of epothilone B that has improved in vivo metabolic stability when compared to its natural precursor. The key difference between ixabepilone and epothilone B is the replacement of the macrolide ring oxygen atom with a nitrogen atom to give the corresponding macrolactam. Ixabepilone has a molecular formula of C27H42N2O5S and a molecular weight of 506.7 grams/mole.

Cytotoxicity against cancer cells in vitro and in vivo.

1. In-vitro cytotoxicity: Ixabepilone has shown broad spectrum of activity against a panel of tumor cell lines in vitro. Of 21 cell lines tested 18 had IC50 values between 1.4 - 6 nM (72 hr exposure). Three cell lines had IC50 values greater than 6 nM: i.e., two highly multi drug resistant (MDR) colon tumor lines HCT 116/VM46 (24.5 nM) and MIP (24 nM), and the normal mouse lung fibroblast cell line MLF (34.5 nM). Ixabepilone did substantially overcome the multidrug resistance inherent in these cell lines. Thus for paclitaxel, the ratios of concentrations (R/S, or resistance ratio) required to inhibit cell growth by 50% in these resistant lines versus those required for the sensitive HCT116 line were 155 and > 55 respectively, for HCT116/VM46 and MIP. In comparison, the R/S ratios for ixabepilone were only 9.4 and 9.5, respectively [19, 20].

2. In-vivo antitumor activity following parenteral administration: Ixabepilone was evaluated in a panel of eight human and murine tumor models. Five were chosen because of their resistance to paclitaxel, and three paclitaxel-sensitive models were included in order to gain a full assessment of the spectrum of antitumor activity of ixabepilone [19, 20].

a. Pat-7: clinically–derived paclitaxel-resistant ovarian cancer model: This tumor model was established from a tumor biopsy of an ovarian cancer patient (Pat-7), who was initially responsive to paclitaxel treatment but ultimately developed resistance to it following nine courses of monotherapy with paclitaxel. Prior to paclitaxel, Pat-7 was treated with carboplatin, cytoxan, VP-16, ifosfamide and altretamine. Ixabepilone was administered to nude mice bearing staged tumors using an every 2 days x 5 schedule. At optimal dose it was highly active eliciting 2.1 and 4.5 LCKs (log cell kills) in two
separate tests. Concomitantly evaluated IV paclitaxel yielded 0.6 and 1.3 LCKs respectively, at optimal dose and schedule.

b. A2780Tax: human ovarian carcinoma xenograft (mutated tubulin): A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. A2780Tax was derived in vitro by selection with paclitaxel and verapamil, and is resistant by virtue of mutations in beta tubulin. Ixabepilone treatment of mice with A2780Tax tumors on an every 2 days x 5 schedule yielded 2.5 LCK at its MTD. By comparison, IV paclitaxel yielded 0.8 LCK at its MTD.

c. HCT 116/VM46: human colon carcinoma xenograft (multidrug resistant): HCT 116/VM46 is a multidrug-resistant colon carcinoma developed from the sensitive HCT116 parent cell line. In nude mice, HCT 116/VM46 has consistently demonstrated high resistance to paclitaxel (median = 0.35 LCK). Ixabepilone treatment of mice bearing staged HCT 116/VM46 tumors produced significant antitumor effects. At its optimal dose, using an every 2 days x 5 schedule ixabepilone yielded 3.1, 1.3 and 1.8 LCKs. In contrast, concomitantly tested IV paclitaxel yielded 0.4 and 0.7 LCKs.

d. Pat-21: clinically-derived paclitaxel resistant breast cancer model: Pat-21 is an early passage paclitaxel-resistant tumor model established from a tumor biopsy of a breast cancer patient with metastatic disease who was given, and failed to respond to an experimental therapy consisting of 5 cycles of paclitaxel in combination with the multidrug reversal agent dextrerapamil. Prior to taxol the patient was treated with adriamycin, cytoxan, methotrexate and 5-FU. For antitumor efficacy of evaluation, two courses of ixabepilone or paclitaxel were administered to mice bearing Pat-21 tumors staged to approximately 100 mg. The two courses were separated by a 3-week interval. Each courses consisted of 3 doses given every 4 days. Paclitaxel was completely inactive against this model yielding 0.3 LCK at its MTD. In contrast, ixabepilone was significantly active, yielding LCK values of > 1.5 at its optimal dose.

e. A2780 human ovarian carcinoma model: A2780 is a fast growing human ovarian carcinoma model that is highly sensitive to paclitaxel. Nude mice bearing staged tumors were treated with ixabepilone using the "paclitaxel-optimized schedule" of IV administration every two days for a total of 5 injections (every 2 days x 5). At the maximum tolerated dose, ixabepilone was highly active, yielding LCKs of > 4.8, 2 and 3.1. Concomitantly tested IV paclitaxel yielded LCKs of 2 and 3.5 at its optimal dose.

Schedule dependency [19, 21]: Several studies have been conducted to evaluate the schedule dependency of ixabepilone:

1. Employing A2780 tumors, ixabepilone was administered to mice by two different schedules: [1] an every 2 days x 5 schedule, previously optimized for paclitaxel and [2] a less frequent every 4 days x 3 schedule. Although both schedules were very active, yielding 2.4 and >5.3 LCKs, respectively, the less frequent dosing schedule allowed a higher dose level to be given (MTD = 16 mg/kg/inj) and performed far better than the more frequent schedule (MTD = 6.3 mg/kg/inj).

2. In the HCT116 human colon carcinoma model, three different schedules of treatment were used: q2d x 5, q4d x 3, as well as q8d x 2. All treatments were IV and the tumors were staged to 100 mg at the initiation of treatment. Best results were obtained with the least frequent treatment schedule, q8d x 2. At the optimal dose of 24 mg/kg/inj, BMS–
247550 produced 100% cures (8 out of 8 mice) with the q8d x 2 schedule, compared with cures in 5 of 8 and 4 of 8 mice with the q2d x 3 and q2d x 5 schedules, respectively.

3. In two other studies employing the Pat-7 and HCT116/VM46 tumors, the efficacy of two IV treatment schedules were compared: q2d x 5 and q4d x 3. In both cases, the two regimens yielded essentially equivalent antitumor activities.

**Kinetics, Distribution, Metabolism and Excretion [19].**

Preclinical pharmacokinetic studies have been conducted with ixabepilone in mice, rats and dogs as separate pharmacokinetic investigations or in conjunction with toxicology/pharmacodynamic studies.

1. Kinetics: Following single IV doses of 10 - 30 mg/kg in rats, the mean CMAX values of ixabepilone had similar ranges in both male and female rats. In both rats (10 - 30 mg/kg single IV dose) and dogs (0.5 to 5 mg/kg single IV dose), dose-related increases in the systemic exposure (CMAX and AUC) of ixabepilone were observed; however the increase was more than proportional to the increase in dose. Furthermore, dose-related increase in systemic exposure to BMS-326412 was also observed. The AUC values of ixabepilone and BMS-326412 (a diole degradation product of) were higher by 1.8- to 2.4-fold and 1.3- to 2.0-fold, respectively, in female rats compared to male rats. Gender effect on the kinetics of could not be conclusively evaluated in the dog due to limited sample size, but the kinetics appeared to be reasonably similar between genders.

2. Distribution: Following IV administration in mice, rats and dogs, mean VSS values were obtained suggesting that ixabepilone undergoes extensive extravascular distribution in these species.

3. Metabolism: Ixabepilone undergoes oxidative metabolism when incubated with mouse, rat, dog and human liver microsomes. The rate of oxidative metabolism and the metabolite distribution appeared to be similar among these species. Qualitatively there appeared to be similar production of metabolites of ixabepilone after incubation with rat or human hepatocytes compared to microsomal incubations. However, products similar to those arising from the chemical degradation of ixabepilone appeared to be the major products in the hepatocyte incubations. *In vitro*, ixabepilone was a weak inhibitor of CYP3A4 [average IC50 value of 7.3 mM (37 mg/ml)], but did not inhibit CYP1A2, CYP2C9, CYP2C19, or CYP2D6 suggesting that ixabepilone may have minimal potential to alter the metabolic clearance of drugs that are highly metabolized by CYP3A4. When ixabepilone was incubated with human liver microsomes along with compounds specific for the inhibition of individual cytochrome P450s, significant (almost complete) inhibition was observed only with the CYP3A4 inhibitors (troleandomycin and ketoconazole), suggesting that ixabepilone may be a substrate for CYP3A4 in humans.

4. Excretion: Following IV administration of ixabepilone in mice, rats, and dogs, the mean T-HALF values were approximately 3, 9.6, and 24 h, respectively. CLT values were 68, 56, and 17.3 mL/min/kg in mice, rats, and dogs, respectively; these values represented 76%, 100%, and 56% of the liver blood flow, respectively. In bile duct cannulated rats that received an intraarterial or oral dose of ixabepilone, negligible (< 1% of the dose) excretion of intact ixabepilone was observed in the bile, and some detectable amount (not quantified due to lack of stability data) of ixabepilone was also observed in the urine.
Single-dose good laboratory practice (GLP) intravenous toxicity studies with ixabepilone were performed in rats and dogs. In addition, a single-dose intravenous exploratory toxicity study in rats and a 5-day intravenous exploratory neurotoxicity study in mice were conducted. In the repeat-dose exploratory neurotoxicity study, ixabepilone and paclitaxel were evaluated together.

1. Single Dose Intravenous Toxicity Study in Rats:
   Ixabepilone was administered intravenously as a single dose to groups of 10 rats at doses of 10, 25, or 30 mg/kg (60, 150, or 180 mg/m²). Systemic exposure to ixabepilone was dose related but greater than dose proportional. A dose-related increase was also observed in systemic exposure to BMS-326412, a diole degradation product of ixabepilone. Females had 1.8- to 2.4-fold and 1.3- to 2.0-fold higher exposures to ixabepilone and BMS-326412 than males, respectively.

   At 10 mg/kg, one female died on day 7. At 25 mg/kg, one male was found dead on day 14 and eight females were found dead or were sacrificed moribund on days 5-9. At 30 mg/kg, nine females were found dead or sacrificed moribund on days 5-13. The intravenous dose of ixabepilone, which was severely toxic to 10% of the rats (STD10), was estimated by linear regression analysis of the mortality data to be 12.3 mg/kg (approximately 74 mg/m²). Morbidity and death were attributed to failure of the immune system associated with drug-related depletion of the bone marrow and lymphoid organs, and to toxic enteropathy.

   Ixabepilone-related clinical effects at all dose levels included dose-dependent increased incidence of thin appearance, hunched posture, chromorhinorrhea, dehydration, stool changes (soft, liquid, and/or mucous), soiling, rough haircoat, ptosis, respiration changes (labored and/or increased), hindlimb paresis, and dose-related decreased mean body weight and food consumption. Additional findings at 25 and 30 mg/kg included decreased activity, swelling (muzzle, tongue and/or limbs), discoloration (white tongue, red mouth and/or pallor), chromodacryorrhea, ataxia, prolapsed penis, absent feces, and sporadic vocalization. Ixabepilone-related clinical signs noted at one or both dose levels prior to death included coolness to the touch, gasping respiration, cyanosis, abdominal swelling, incoordination, lameness, and oral lesions.

   At all doses on days 6 and 7, drug-related clinicopathologic changes consisted of decreases in white-blood cell counts (due to absolute neutropenia and moderate lymphopenia), eosinophils, platelets, mean corpuscular volume, reticulocytes, total protein, and albumin; and increases in mean corpuscular hemoglobin concentration, prothrombin time, activated partial thromboplastin time, and fibrinogen. Also on day 6, albumin-to-globulin ratio was decreased at 25 and 30 mg/kg, and globulins and aspartate aminotransferase were increased at 30 mg/kg. On day 14, hematologic values had recovered to normal or were increased (rebound) and urea nitrogen was increased at 30 mg/kg. At the day 7 necropsy, drug-related gross gastrointestinal changes, decreases in thymus, spleen and testes weights/size, and increases in adrenal gland weights were noted at all doses, and skin and lymph node changes were noted at 30 mg/kg. On day 29, testes weights were decreased at all doses, and spleen weights were decreased at 30 mg/kg.

   Histopathologic findings observed at all doses on day 7 and/or at early death necropsies included lymphoid necrosis/depletion of thymus, spleen and lymph nodes;
depletion (hypocellularity) or myeloid hyperplasia of the bone marrow; gastrointestinal inflammatory lesions; axonal degeneration of the peripheral nerve and spinal cord; degeneration of testes and epididymis; hyposperma; single-cell necrosis of corneal and hair follicle epithelium; and a secondary change of adrenocortical cell hypertrophy (due to stress). Additionally, inflammatory lesions of the skin and lymph nodes secondarily related to depression of the immune system were observed in some females at 25 and 30 mg/kg. Histopathologic findings noted at all doses from animals necropsied on day 29 consisted of axonal degeneration of peripheral nerve and spinal cord, degeneration of testes and epididymis, and hyposperma.

In conclusion, the STD10 was estimated to be 12.3 mg/kg (approximately 74 mg/m²). The major clinical and histopathologic effects were consistent with those of other microtubule-stabilizing anticancer agents and included bone marrow and lymphoid depletion, peripheral neuropathy, and gastrointestinal and testicular toxicity.

2. Single Dose Intravenous Toxicity Study in Dogs:

Ixabepilone was administered as a single intravenous infusion (2 ml/min) to groups of two male and two female dogs at 0.5 or 5 mg/kg (10 or 100 mg/m², respectively). Systemic exposure to ixabepilone was dose related but greater than dose proportional. A dose-related increase was also observed in systemic exposure to BMS-326412, a diole degradation product of ixabepilone. There were no apparent sex-related differences in ixabepilone exposure in dogs.

All dogs receiving 5 mg/kg died or were sacrificed in moribund condition on day 3, exhibiting drug-related clinical signs including bloody emesis, dehydration, pallor, red liquid stool, prostration, whole-body tremor, labored respiration, soiling, and salivation. Blood samples for clinical pathology were not obtained from these animals. Anatomic pathology findings included decreased thymus size (one male) and dark discoloration of the stomach (one female), small and large intestine, and lymph nodes. Drug-related findings at 0.5 mg/kg included minimal reversible decreases in leukocyte and/or platelet counts in one male and one female. Clinical signs related to administration of the Cremophor EL/ethanol vehicle were consistent with anaphylactoid reaction and occurred in all groups including the vehicle control.

In conclusion, ixabepilone produced severe toxicity and death when administered intravenously to dogs at 100 mg/m², a dose higher than the single dose of 74 mg/m² that was severely toxic to 10% of rats (STD10) in a previous study. Deaths were attributed to severe gastrointestinal toxicity characterized by red emesis and liquid stool, secondary dehydration, and discoloration of the gastrointestinal tract. A dose of 10 mg/m² (equivalent to 1/7 the rat STD10) was associated with only transient leukopenia and/or thrombocytopenia in one male and one female dog.

Special Toxicity Studies [19].

1. Five-Day Intravenous Exploratory Neurotoxicity Study in Mice:

Peripheral neuropathy was observed in an ixabepilone single-dose intravenous exploratory study in rats, an expected finding since epothilones have a similar mechanism of action as taxanes, which are known to cause neuropathies. An additional study was conducted to investigate and compare the peripheral neurotoxic potential of ixabepilone with paclitaxel, when administered at their respective maximum tolerated doses. Groups of five female mice were administered ixabepilone at 4.8 mg/kg (14.4 mg/m²) or paclitaxel at 48 mg/kg (144 mg/m²), intravenously daily for 5 days. Additional groups of five female mice served as vehicle controls and received either ethanol: water
or Cremophor® EL:ethanol:saline (ixabepilone and paclitaxel vehicles, respectively). All animals were necropsied on day 7 post-dose.

Hindlimb paresis, indicative of peripheral neuropathy, was clinically observed in both treatment groups and was slightly more severe in the paclitaxel group. Axonal degeneration of the sciatic nerve was observed by light microscopy in animals from both treatment groups, correlating with the clinical signs of hindlimb paresis. The severity of axonal degeneration was equivalent for ixabepilone and paclitaxel.

Results from this study indicate that ixabepilone and paclitaxel, when administered at their respective maximum tolerated doses, induce peripheral neuropathy in mice that is similar in nature and severity.

Clinical Studies.
Ixabepilone phase I testing in humans.

Three different schedules have been tried. A bolus regimen every three weeks established 50 mg/m² as the MTD, with neurotoxicity and neutropenia as dose limiting toxicities. In a trial with weekly administration, investigators were able to administer weekly doses of 30 mg/m², with neurotoxicity noted, although adjustments to the schedule were needed. A phase I study was designed to establish a phase II dose of BMS–247550 administered as a 1 hr infusion on days 1 to 5 every 21 days. Initially, 27 patients were enrolled [21]. Twenty -one of these 27 patients had received prior taxane therapy; including five who had received prior Taxol® or Taxotere® less than six months prior to receiving ixabepilone. Dose levels included 1.5, 3, 6 and 8 mg/m²/d administered on each of five successive days. Intra-patient dose escalation without/with GCSF was permitted if dose-limiting toxicity (DLT) was not observed in the previous cycle. All three patients receiving 8 mg/m2/d without GCSF in cycle 1 experienced neutropenia as the DLT. 6 mg/m²/d was identified as the maximum tolerated dose (MTD) without GCSF, and is the recommended phase II dose. A dose ≥ 8 mg/m²/d was administered in 48 cycles to 20 pts. All patients received a dose ≥ 6 mg/m²/d either initially or after intra-patient dose escalation. A total of 102 cycles were administered (median of 3 per patient; with 13 patients receiving ≥ 4 cycles). Ninety-nine of the 102 cycles were given at a dose ≥ 6 mg/m²/d. Non-hematologic grade 3 toxicities included: fatigue (7 cycles), stomatitis (2 cycles) and anorexia (1 cycle). All other non-hematologic toxicities were grade 2 or less including neurotoxicity in 17 patients. Pharmacokinetics indicates steady state is reached by day 3, with Cmax and Cmin values suggesting no accumulation (day 5 vs. day 1). Additional parameters include: a t₁/₂α of 115 ± .062 hours, a t₁/₂β of 12.7 ± 4.4 hours, a Vdₘₘ of 8.08 ± 3.99 L/kg, and a clearance of 419 ± 123 ml/min/m². A partial response was observed in 5 patients including two patients with breast cancer, two patients with cervical cancer and one patient with basal cell carcinoma; with > 50% reduction in CA125 in two of 12 patients with advanced ovarian cancer (all breast, cervical and ovarian cancer patients had prior taxane therapy). Hypersensitivity reactions have not been observed using a premedication regimen consisting of H1 and H2 antagonists without steroids prior to each dose of ixabepilone. We conclude that a dose of 6 mg/m²/d x 5d of ixabepilone is well tolerated, and clinically active in patients with cancer who have previously received taxane therapy.

Based on the presence of Cremophor® EL in the formulation of ixabepilone, the potential for hypersensitivity reactions exists with intravenous administration of this compound. Although the quantity of Cremophor® EL in ixabepilone is equivalent to three times that in the same dose of Taxol®, its greater potency has resulted in a Cremophor®
EL to total volume that is less than that achieved when Taxol®, which includes Cremophor® EL in its formulation, has been administered. In clinical trials, anaphylaxis and severe hypersensitivity reactions (dyspnea, hypotension requiring treatment, angioedema, and generalized urticaria) have occurred in 2% of patients receiving Taxol®. It is not known whether the hypersensitivity reaction is due to paclitaxel, Cremophor® EL, or both. The reported incidence of anaphylaxis with other Cremophor® EL-containing compounds is much lower than with Taxol® [22]. For example, cyclosporine for injection has rarely been associated with anaphylactic reactions (approximately 1 in 1,000). Although the low incidence of anaphylactic reactions with Cremophor® EL-containing compounds other than Taxol®, suggest this may not be a significant problem, some cases of hypersensitivity have been reported with ixabepilone and consequently, routine premedication will be used in this trial. Prophylaxis for hypersensitivity reactions will be similar to the “standard” Taxol® premedication regimen but will not include steroids. It will consist of the following: (1) diphenhydramine 50 mg IV, 30 to 60 minutes before the administration of ixabepilone; and (2) cimetidine 300 mg or ranitidine 50 mg IV, 30 to 60 minutes before the administration of ixabepilone.

Ixabepilone has demonstrated single-agent activity against a wide variety of solid tumors, including breast cancer (early- and late-stage disease) [23], NSCLC [24], pancreatic cancer [25], renal cell cancer (RCC) [26], prostate cancer [27], and lymphoma [28]. The majority of these studies involved tumors that were heavily pre-treated.

Ixabepilone in renal cell carcinoma. In addition to these studies in tumors with acquired resistance to chemotherapy, ixabepilone has also been shown to have activity in the treatment of cancers that are typically considered chemotherapy resistant. Ixabepilone has activity in RCC, suggesting that this agent may represent a treatment option even for this highly refractory disease that is known to be one of the tumors with the highest levels of endogenous MDR [29]. No chemotherapy has been proven effective in renal cell cancer (RCC). In this study, patients with metastatic RCC received ixabepilone (6 mg/m²/day), daily for 5 consecutive days every 3 weeks. All patients had been previously treated with, been ineligible for, or refused IL-2 treatment. Ixabepilone was continued until progression or unacceptable toxicities. 590 cycles have been administered in 87 patients. Treatment was well tolerated. A CR has been confirmed in one patient and PR has been confirmed in 10 patients with clear cell RCC (2 patients with PR had a combination of clear cell and sarcomatoid mixed histology). The overall response rate was 13%. The median duration of response was 5.5 months. Treatment related toxicity was primarily grade 1/2, including neutropenia and neurotoxicity. No correlation between VHL status and drug-activity has been observed.

1.2.3 RENAL CELL CARCINOMA.

Renal cell carcinoma (RCC) is diagnosed in approximately 170,000 patients worldwide annually, resulting in 82,000 deaths [30]. Many patients present with advanced or unresectable disease, and up to 30% of patients treated by nephrectomy for localized disease will relapse [3]. The 5-year survival rate for metastatic RCC is estimated to be ≤ 10% [1, 4, 5]. Hormonal, chemotherapeutic, and radiation therapy approaches have failed to significantly improve clinical outcomes for patients with metastatic disease.

Nephrectomy may be curative in cases of renal cell cancer without metastases. Patients with metastatic RCC also benefit from the cytoreductive effects of nephrectomy. The time to tumor progression (TTP, 5 versus 3 months) and overall survival (OS, 17
versus 7 months) were improved in an EORTC study comparing nephrectomy followed by Interferon-α (IFN-α) versus IFN-α alone. A survival advantage of nephrectomy in addition to IFN-α, 11 months versus 8 months, was confirmed in a similar study reported by SWOG [31,32]. Cytokine therapies have been commonly used in the treatment of metastatic RCC but with limited anti-tumor effect. IFN-α has an approximately 11 – 15% objective response rate in appropriately selected individuals. In general, these patients have non-bulky pulmonary and/or soft tissue metastases with good performance status (ECOG performance status 0 or 1) without weight loss. These responses are rarely complete or durable, but the results of two randomized studies suggest that IFN-α improves survival [36].

Administration of high dose interleukin-2 (IL-2) appears to have a similar overall response rate to IFN-α, but with approximately 5% of the appropriately selected patients having durable complete remissions. The optimum dose of IL-2 is unknown. High-dose therapy has been approved by the Food and Drug Administration in the United States, and while it appears to be associated with higher response rates, the incidence of toxic effects is also high [37]. Low-dose IL-2 regimens produce lower response rates but can be administered with fewer toxic effects, especially hypotension [38]. Combinations of IL-2 and IFN-α have been studied, but have not shown an overall survival advantage over monotherapy and are associated with significant toxicity [39].

Chemotherapeutic agents have been extensively studied in patients with metastatic RCC, but no single agent or combination has been found to be beneficial. Studies of chemotherapy combined with cytokine therapy have also been discouraging [40]. There is clearly an unmet medical need in the treatment of patients with metastatic RCC.

Seventy-five to 85 percent of RCCs are highly vascularized tumors that over-express a number of growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) [41,42]. In addition, RCC tumors over-express the receptors for these peptides. These ligands and receptors may be involved in the autocrine stimulation of tumor cell growth, or in the paracrine stimulation of neovascular or stromal fibroblast growth that supports tumor expansion. A treatment that specifically interrupts these signalling pathways may have significant anti-tumor activity.

Based on these pre-clinical observations, several anti-angiogenic compounds have been successfully investigated. Sorafenib, an oral inhibitor of VEGFR, PDGFR and RAF kinases, has demonstrated clinical efficacy in metastatic RCC in a large phase II and a randomized phase III trial. The randomized phase III trial demonstrated that the median duration of progression-free survival was 24 weeks in sorafenib patients compared with 12 weeks in the placebo group (P < .000001; hazard ratio 0.44). The response data demonstrated that 80% of patients were progression free in the sorafenib arm (2% partial response and 78% stable disease) compared with 55% in the placebo arm (0% partial response and 55% stable disease). The median overall survival was 19.3 months for sorafenib and 15.9 months for placebo when censored for patients on the placebo arm who crossed over to sorafenib. These data did not attain a level of significance at this interim analysis, but a favorable trend in survival benefit was observed [43,44,45].

Sunitinib® and its active metabolite are selective inhibitors of multiple receptor tyrosine kinases associated with tumor growth and angiogenesis [46]. The clinical
The efficacy of oral sunitinib has been demonstrated in patients with renal cell carcinoma. In two multi-center, single-arm, phase II clinical trials in patients with cytokine-refractory metastatic RCC, partial responses were reported in 40% and 43% of patients receiving sunitinib 50 mg/day for 4 weeks followed by 2 weeks without treatment in 6-week cycles; 27% and 22% of patients achieved stable disease for ≥ 3 months. In a phase III trial in previously untreated patients, sunitinib was more effective than interferon-alpha as a first-line therapy in patients with metastatic RCC. The progression-free survival was 11 months for sunitinib versus 5 months for IFNα (hazard ratio 0.415; p < 0.0001). The response rate was 31% for sunitinib versus 9% for IFNα (p < 0.000001) [47,48]. Overall survival data from this trial are not yet mature.

The FDA approved sorafenib (Nexavar®) and sunitinib (Sutent®) in December 2005 and February 2006 respectively based on objective responses and improvement in progression-free survival [49]. In May 2007, the FDA approved the mTOR inhibitor temsirolimus (Torisel®), based on improvement in survival in a randomized trial against interferon although there was no difference in response rate. This was the first agent to show a survival advantage since IL-2. The median survival improved from 7.3 months in the interferon group to 10.9 months in the temsirolimus group [50]. However, it should be noted that, although the drug was administered to patients who had received no prior systemic therapy, the study only included patients with a poor prognosis based on presence of 3 of 6 predictors of short survival.

1.2.4 PRE-CLINICAL DATA: BEVACIZUMAB AND IXABEPILONE

Antitumor activity was evaluated in human renal clear cell carcinoma xenograft 151B in mice. All mice were purchased from Harlan Sprague Dawley (Indianapolis, IN). Tumors were propagated as subcutaneous (SC) transplants in nude mice using tumor fragments taken from donor mice. Eight female mice were used for each experimental test condition. In this animal model, compounds were administered and evaluated at the maximum tolerated dose (MTD) that is defined as the dose level immediately below which excessive toxicity (i.e. more than one death) occurred. The MTDs in this study were determined to be: ixabepilone (6 mg/kg IV every 4 days for 3 doses), bevacizumab (4 mg/kg IV every 4 days for 3 doses), and sunitinib (40 mg/kg IV every day for 14 doses). The compounds were evaluated for tumor response as single agent therapy or in combination to assess synergy. Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reached a predetermined "target" size. Tumor weights (mg) were estimated from the formula:

\[ \text{Tumor weight} = \frac{(\text{length} \times \text{width}^2)}{2} \]

Tumor response end-point was expressed in terms of tumor growth delay (T-C value), defined as the difference in time (days) required for the treated tumors (T) to reach a predetermined target size compared to those of the control group (C). Results are presented in the following figures:
Combination of Ixabepilone with Anti-angiogenics
Comparison of Bevacizumab and Sunitinib in the 151-B Renal Carcinoma

Both ixabepilone plus bevacizumab and ixabepilone plus sunitinib are synergistic. Ixabepilone plus sunitinib was associated with increased weight loss, and dose reduction was required. However, at MTDs, both combinations produced similar degree of synergism.

1.2.5 RATIONALE FOR COMBINATION: BEVACIZUMAB AND IXABEPILONE

Single-agent bevacizumab and ixabepilone have demonstrated activity in metastatic renal cell carcinoma. Extensive phase II and III studies suggest the absence of overlapping toxicities between bevacizumab and ixabepilone. Development of a well-tolerated and active combination has the potential for further improvement in the treatment of a large spectrum of tumor types including renal, breast, prostate and ovarian cancer.

Substantial preclinical data support this combination. First, in vivo synergistic activity between ixabepilone and bevacizumab has been demonstrated. Using the 151-B human renal carcinoma xenograft model, ixabepilone combined with a VEGFR inhibitor (sunitinib), or anti-VEGF (bevacizumab) demonstrates higher activity compared to a single administration. Second, preclinical data support the interest of combining cytotoxics and antiangiogenics. By additionally “normalizing” tumor vasculature and reducing tumor interstitial fluid pressure, VEGF antagonists may enhance intratumoral delivery of traditional cytotoxic agents thereby improving their antitumor efficacy without overlapping toxicity. Interference with endothelial cell recovery after cytotoxic damage has also been reported. In addition, CD11+ myeloid cells are involved in refractoriness to anti-VEGF therapy. This cell subpopulation is highly sensitive to cytotoxics and support the use of drug combinations to overcome antiangiogenic resistance. Convincing clinical evidence in support of this therapeutic approach was first demonstrated by bevacizumab, for the first-line treatment of patients with metastatic carcinoma of the colon, breast, non-small cell lung carcinoma or even recurrent glioblastomas.
Metastatic renal cell carcinoma remains an incurable disease for which new and improved treatment options are still desperately needed. Results obtained with antiangiogenics in mRCC must be improved. Several directions are currently under investigation, including concomitant or sequential administration of angiogenic inhibitors, combination with immunotherapy such as cytokines or adoptive immunotherapy. This study will investigate the role of a potent cytotoxic (ixabepilone) in this chemotherapy-resistant tumor combined with one of the more effective molecules (bevacizumab) studied in mRCC. Furthermore the efficacy of systemic therapies is very limited after front-line treatment failure with “antiangiogenic agents”. In bevacizumab-refractory patients, sunitinib has demonstrated a 23% response rate (n = 61 patients). After sunitinib failure, sorafenib has limited efficacy with an 18% response rate (N = 18), with a limited duration of response (22 weeks). The activity of bevacizumab, used as a single-agent, has not been explored after VEGFR inhibitors failure. The objective of this study is to demonstrate the activity of the combination in second-line therapy after sunitinib or sorafenib failure (or both compounds). The hypothesis is to reach an objective response rate superior to 25%.

Finally, predictive factors of activity for angiogenic inhibitors need to be determined. Added to this clinical trial, correlative studies will investigate the value of signals following bevacizumab and ixabepilone administration. This program will investigate the value of tumor or blood biomarkers including circulating endothelial cells, serum or tumor proteins involved in the angiogenic process (VEGF and VEGF-independent pathways), and evaluation of drug distribution and tumor blood flow by PET imaging or dynamic imaging (see Section 6.3 and Appendix 15.A).

1.2.5.1 Dose and design rationale.

In this combination phase II study, the starting dose and dosing interval of ixabepilone (6 mg/m² daily x 5 days) will be defined as the regimen used in the ongoing phase II study conducted in our institution in mRCC. This regimen has demonstrated a 13% response rate (RECIST criteria) in 87 patients with an acceptable profile of toxicity. Based on the ixabepilone regimen, bevacizumab will be subsequently given every 3 weeks at the recommended dose of 15 mg/kg. This is the schedule used in combination with taxol, carboplatin and taxol, in the breast cancer and NSCLC studies respectively. The proposed dose and schedule have not been previously explored in a phase 1 study. Thus, demonstration of acceptable safety for the first 6 patients enrolled in this study will be a prerequisite for enrolling subjects into the full cohort of patients. This combination will be evaluated in a second line therapy of mRCC, after the failure of the standard therapy approved in this indication. We hypothesize, regarding the mechanism of action of ixabepilone and bevacizumab and their synergistic activity demonstrated in vivo, that acquired resistance to VEGFR inhibitors or mTOR inhibitors will not jeopardize the activity of this combination.

If no more than 6 responses are observed among the initial 33 patients, the study will be terminated.

2. ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Inclusion criteria.

Subjects meeting all of the following criteria will be considered for enrollment into the study:
1. Metastatic or unsectable renal cell carcinoma with predominant clear cell histology (>70%).
2. Progression on or after stopping treatment with a VEGF receptor tyrosine kinase inhibitor (sunitinib and/or sorafenib). Patients must have received one or both agents (sunitinib and/or sorafenib). Prior IL-2, interferon treatment and/or m-TOR treatment is allowed, but not mandatory. Patients must be off of prior therapy for at least 4 weeks prior to entry.
3. Eighteen years of age or older.
4. ECOG performance status ≤ 2.
5. Resolution of any toxic effects of prior therapy (except alopecia) to active version of CTCAE grade ≤ 1 and to baseline laboratory values as defined in inclusion criterion # 6.
6. Adequate organ and bone marrow function as evidenced by:
   - hemoglobin ≥ 9.0 g/dL
   - absolute neutrophil count ≥ 1.5 x 10^9/L
   - platelet count ≥ 100 x 10^9/L
   - creatinine ≤ 1.5 x ULN, and proteinuria ≤ 500 mg/24 hours
   - AST/SGOT and ALT/SGPT ≤ 2.5 x ULN (or ≤ 5 x ULN if liver function abnormalities due to underlying malignancy)
   - total bilirubin ≤ 1.5 x ULN
7. Subjects must be postmenopausal, surgically sterile, or using effective contraception. All female subjects of childbearing potential must have a negative pregnancy test (serum or urine) within 7 days prior to enrollment. Effective contraception includes hormonal or barrier methods.
8. No other invasive malignancies within the past two years (with the exception of non-melanoma skin cancers, non-invasive bladder cancer, stage I endometrial cancer or cervical cancer).
9. Subjects must agree to sign and date an Institutional Review Board (IRB)-approved subject informed consent form.
10. Subjects must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
11. Patients must have measurable disease either by conventional imaging or clinical examination.

2.2 Exclusion criteria.
Subjects presenting with any of the following will not be included in the study:

1. Invasive procedures defined as follows:
   - Major surgical procedure, open biopsy or significant traumatic injury within 6 weeks prior to Day 1 therapy
   - Anticipation of need for major surgical procedures during the course of the study
   - Minor surgery, such as port-a-cath placement, and dental procedures, within 2 weeks.
   - (There will be no delay for percutaneous core biopsies or PICC/IJ line placement)
2. Cumulative radiation therapy to > 25% of the total bone marrow.
3. History of uncontrolled or labile hypertension, defined as blood pressure > 160/90 mm Hg, on at least 2 repeated determinations on separate days within 15 days prior to study enrollment.

4. Any of the following within 6 months prior to study enrollment: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure; cerebrovascular accident or transient ischemic attack, grade ≥ 2 peripheral neuropathy, peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, or other thromboembolic event.

5. Symptomatic spinal cord compression.

6. Evidence of clinically significant bleeding diathesis or underlying coagulopathy.

7. Antiretroviral therapy for HIV disease.

8. Pregnant (positive pregnancy test) or nursing women. Both fertile men and women must agree to use adequate contraceptive measures during study therapy and for at least 6 months after the completion of bevacizumab therapy.

9. Other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the subject's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.

10. Prior therapy with bevacizumab
11. Prior therapy with ixabepilone.
12. Patients on anticoagulant therapy will be evaluated on a case by case basis for inclusion.

13. History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to day 1

14. Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1

17. Known CNS disease except for treated brain metastasis. Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 3 months, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose of anticonvulsants are allowed). Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.

18. Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies
19. Patients receiving CYP3A4 inhibitors in section 3.6 that can not be discontinued.

2.3 Baseline evaluation.

Complete history and physical examination (including height, weight, vital signs including blood pressure, and ECOG performance score) with documentation of

1) Measurable disease, detailed sites of tumor
2) Narcotic use and pain assessment and
3) Prior therapies (surgical, radio therapeutic, and molecular-targeted therapies). Baseline blood pressure will be documented on physical exam on initial screening and confirmed by blood pressure reading on the day of therapy starts. A complete medication history will be obtained prior to starting, including over the counter medications, homeopathic remedies, vitamins, and alternative therapies.

Medically Indicated Imaging Studies (Baseline) –
- CT scan of brain, chest, abdomen and pelvis within 16 days of enrollment; areas of known or suspected disease involvement prior to receiving treatment to be used to monitor response.
- In some patients an MRI, PET, or ultrasound may be more appropriate and may be ordered or requested in addition the baseline CT scan. This must be completed within 16 days of enrollment.
- An EKG should be obtained within 16 days of enrollment.
- Laboratory Evaluation [baseline is to be obtained within 4 days prior to enrollment].

Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time.
Biochemical Profile: Serum electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, magnesium, amylase, lipase. Urine beta-hCG for female patients of childbearing age and anatomic ability. For those women who have undergone hysterectomy this will not be a requirement.
Spot UPC for protein and creatinine.
A block of primary tissue (or 10 unstained sections on charged slides) from the time of diagnosis will be required from each patient. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable. This will be used for the mandatory internal pathological review to confirm diagnosis, performed in Cancer Center USA’s Pathology Department.

3.0 STUDY IMPLEMENTATION
3.1 Study Design

Cycle one:
Obtained within one week prior to study entry, unless otherwise indicated:
- History and physical examination.
- Laboratory studies: CBC with differential, platelet count, and CHEM20 Panel.
- Imaging studies: CT or MRI (obtained within 16 days prior to study entry).

Every restaging cycle (following the second, fourth and sixth cycles, and then every third cycle):
- History and physical examination (for medical record only; not for Research record), blood pressure patient diary analysis.
- Laboratory studies: CBC with differential, platelet count, and CHEM 20 Panel.
- Imaging studies: CT or MRI of known/suspected areas of disease

Every cycle:
- History and physical examination (for medical record only; not for Research record).
• Laboratory studies: CBC with differential, platelet count, and CHEM20 Panel and Urine Protein:Creatinine (UPC) ratio.

Weekly treatment monitoring:
• CBC with differential and platelet count will be obtained weekly unless the ANC falls below 500 cells/mm$^3$ or the platelet count falls below 50,000 cells/mm$^3$, in which case every attempt should be made to obtain counts every other day until the ANC is above 500 cells/mm$^3$ and the platelet count is above 50,000 cells/mm$^3$.

Safety analysis of the first 6 patients:
In the absence of phase I data, the first 6 patients enrolled in this study will be extensively monitored for safety during the first cycle in addition to the tests required above:
• Weekly call to the patient with specific questions regarding blood pressure and neuropathy symptoms.
• CBC, platelet count will be obtained weekly.
• CHEM20 panel will be obtained weekly
• Daily blood pressure monitoring, recorded in a diary

Toxicity will be analyzed for the first cycle of the first six patients before enrolling further patients. In the absence of clinically significant, unexpected toxicity that requires a therapeutic intervention, we will continue to enroll. In the event of clinically significant, unexpected toxicity that requires an intervention, we will consult with the sponsor and the IRB to determine the course of action. Clinically significant unexpected toxicities include, but are not limited to, Grade 4 (non-hematologic). These first 6 patients will monitor their blood pressure daily x 6 weeks (2cycles). Following the completion of cycle 2, they may begin 3 times per week blood pressure monitoring consistent with the other accruing patients.

All patients:
The doses on this trial will be bevacizumab 15 mg/kg IV every 3 weeks (day 1 of all cycles and ixabepilone administered daily as a one-hour infusion on five successive days (day 1 to day 5, every three weeks at a starting daily dose of 6 mg/m$^2$/day, for a total per cycle dose of 30 mg/m$^2$. A cycle consists of 3 weeks or 21 days. At the outset of the study, the patient may be admitted to the inpatient service to complete research studies including biopsies. Otherwise, treatment will be administered as an outpatient basis. All patients following the initial first six, will monitor their blood pressure at home 3 times a week and record the results in a diary, which they will be instructed to bring to clinic for review.

Duration of Therapy
There is not a preset number of cycles planned per patient. Patients will continue on study as long as they do not meet off-study criteria, they desire to continue and the investigator determines it is safe to continue.
Reassessment.
Patients will be seen in clinic at least every 3 weeks. A history and physical with sphygmonanometry and a review of systems that documents coagulopathy-related events must be charted in the medical record for each visit.

Medically indicated CT scans will be obtained and reviewed approximately every 6 weeks (or 2 cycles of therapy) to monitor disease response. Measurable disease will be monitored as described in section 9. Treatment for each odd number cycle, starting with cycle 3, cannot be given prior to restaging imaging.

Blood pressure monitoring will be based on our current and successful experience (in phase 2 and 3 trials), and on published recommendations. Each patient will receive a sphygmonanometer to use to measure blood pressures at home when outside of the clinical center. Blood pressures will be measured and recorded daily for the first six weeks of therapy for the first six patients. All patients following the initial first 6 patients will monitor and record their blood pressure 3 times per week. The PI will be notified of any abnormal measurement (any systolic BP over 140 or diastolic BP > 90). Treatment will be determined by the BP reported over the 3 weeks period reported in the patient’s diary as well as the BP on the day of reassessment (see section 5.1 for specifics).

3.2 Drug administration

3.2.1. Bevacizumab administration
On the day of bevacizumab administration, a review of systems pertinent to bleeding and thrombosis, a spot urine protein/creatinine ratio, and a measurement of blood pressure should be performed. Dose timing adjustments are listed in section 5. Bevacizumab will be administered intravenously every 3 weeks on an outpatient basis with the exception of admissions for the purpose of facilitating research studies. The dose of bevacizumab to be given is 15 mg/kg.

Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection. Administration will be as a continuous IV infusion. The initial bevacizumab dose will be delivered over 90 ± 10 minutes as a continuous IV infusion. If the first infusion is tolerated without infusion-associated adverse events (fevers and/or chills), the second infusion maybe delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions maybe delivered over 30 minutes.

In the event of an infusion-related event, the infusion of bevacizumab should be stopped and held until resolution of acute symptoms. The PI or AI will be notified of the infusion-related event at the time of the occurrence. Upon resolution, the infusion should be restarted at a rate to increase the total infusion time by 30 minutes beyond the current time. For example, if an infusion related event occurs when the dose is planned to run for 60 minutes (i.e. a rate of 1.7 cc/hr), the drug should be held. When the event is resolved, the rate should be lowered to 1.1 cc/hr.

Special Precautions/Safety Issues:
- Prior to each treatment, the patient should be carefully assessed with special
attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and RPLS. Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in (provide section reference).

- Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

- **Infusional reactions**: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

- **Hypertension**: Patients should have BP monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal BP control according to standard public health guidelines. Please refer to section 3.3.1 for dose modification information related to hypertension.

- **Proteinuria**: Proteinuria should be monitored by urine protein:creatinin (UPC) ratio or dipstick at least every 3 weeks.

- **Surgery and wound complication issues and surgery**: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

### 3.2.2. Ixabepilone administration.

Ixabepilone will be given on a days 1, 2, 3, 4, and 5 of each three week cycle as a one hour intravenous infusion. The dose will be 6 mg/m²/day on five successive days. Ixabepilone is an irritant and may be administered via peripheral or central line. Central lines will be recommended, but not absolutely required for each infusion.

**Premedication**: All subjects must be premedicated before each treatment with ixabepilone to prevent a hypersensitivity reaction. Regimen 1 described below is the premedication regimen recommended for routine use.

**Regimen 1**: Premedicate approximately one hour prior to the infusion of ixabepilone with:

a) Oral H₁ antagonist (may consist of diphenhydramine 50 mg or equivalent H1 antagonist) and
b) Oral H₂ antagonist (may consist of ranitidine 150-300 mg or cimetidine 300-800 mg or nizatidine 150-300 mg or famotidine 20-40 mg or other H₂ antagonist)

(In the event of subject does not tolerate the antihistamines specified, alternatives may be substituted at the Investigator’s discretion. In addition, if the specified antihistamine is not available, alternatives may be substituted including IV formulations)

If a subject experiences a hypersensitivity reaction with oral H₁ and H₂ blockers (Regimen 1) then the subject, if re-treated, should be premedicated according to the recommended regimen below:

**Regimen 2:** Premedicate approximately 30 - 45 minutes prior to each infusion of ixabepilone with:

- a) Dexamethasone 20 mg IV (or equivalent)
- b) Diphenhydramine 50 mg IV (or equivalent), and
- c) Ranitidine 50 mg IV (or equivalent).

If a subject continues to experience a HSR with Regimen 2 then the subject, if retreated, should be premedicated according to the recommended regimen 3:

**Regimen 3:** Premedicate with:

- a) Dexamethasone 20 mg po administered, approximately 12 and 6 hours prior to the infusion of ixabepilone,
- b) Diphenhydramine 50 mg IV, approximately 30 - 45 minutes prior to each infusion of ixabepilone,
- c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent), approximately 30 - 45 minutes prior to each infusion of ixabepilone.

A suggested approach for retreatment with ixabepilone after a Grade 2 or greater HSR despite premedication with Regimen 1, 2 or 3 is as follows:

**Regimen 4:**

- Dexamethasone 20 mg IV or p.o. (or equivalent) every 6 hours for 4 doses with the last dose administered 30 minutes before rechallenge with ixabepilone;
- With the last dexamethasone dose begin:
  - Diphenhydramine 50 mg IV (or equivalent) 30 minutes before ixabepilone,
  - Cimetidine 300 mg or ranitidine 50 mg IV (or equivalent) 30 minutes before ixabepilone.
- Begin ixabepilone at 25% of the previous rate for 1 hour;
- Increase rate gradually to complete the total infusion within 6 hours from the time the drug was initially diluted.

### 3.2.3. Schedule of administration.

On day 1 of cycle 1 (and all subsequent cycles), both bevacizumab and ixabepilone are planned to be administered. The schedule of administration is following:

- Ixabepilone pre-medication,
- Immediately followed by bevacizumab
- Immediately followed by ixabepilone
Patients will be monitored closely for toxicity. Bevacizumab and ixabepilone dose may be adjusted according to individual patient tolerance.

### 3.3 Dose Modifications

#### 3.3.1 Bevacizumab-related toxicities: Dose Modifications/Delays guidelines

Note: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below.

<table>
<thead>
<tr>
<th>Event</th>
<th>CTCAE (active version) Grade</th>
<th>Action to be Taken</th>
</tr>
</thead>
</table>
| **Allergic reactions, or Acute infusional reactions/ cytokine release syndrome** | Grade 1-3 | \n
Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) should discontinue bevacizumab. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. |
| **Congestive Heart Failure** | Grade 3 (symptomatic) | Discontinue bevacizumab |
| | Grade 4 | Discontinue bevacizumab |
| **Proteinuria** | [Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab] | \n
<table>
<thead>
<tr>
<th>UPC ratio</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.5</td>
<td>Continue bevacizumab.</td>
</tr>
</tbody>
</table>
| \n
<table>
<thead>
<tr>
<th>UPC ratio</th>
<th>Action</th>
</tr>
</thead>
</table>
| \n
| Grade 4 or nephrotic syndrome | Discontinue bevacizumab. |
| **Hemorrhage (CNS or pulmonary)** | Grade 2-4 | **Discontinue bevacizumab** |
| **Hemorrhage (other)** | Grade 3 (non-CNS or non-pulmonary) G1 (CNS or pulmonary) | \n
- Patients receiving full-dose anticoagulation should discontinue bevacizumab. 
- For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:
  - the bleeding has resolved and Hb is stable
  - there is no bleeding diathesis that would increase the risk of therapy
  - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.
- Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy. |
<table>
<thead>
<tr>
<th>Event</th>
<th>CTCAE (active version) Grade</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome)</td>
<td>Grade 4</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Wound dehiscence requiring medical or surgical intervention</td>
<td></td>
<td>• Discontinue bevacizumab upon diagnosis of RPLS.</td>
</tr>
<tr>
<td>Perforation (GI, or any other organ)</td>
<td></td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Fistula (GI, pulmonary or any other organ)</td>
<td></td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>G2 requiring medical intervention</td>
<td>• Hold bevacizumab until complete resolution</td>
</tr>
<tr>
<td></td>
<td>G3-4</td>
<td>• Hold bevacizumab until complete resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator’s discretion</td>
</tr>
<tr>
<td>Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).</td>
<td>Grade 3</td>
<td>• Hold bevacizumab until symptoms resolve to &lt; grade 1</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>• Discontinue bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to &lt; grade 1 and unlikely to recur with retreatment.</td>
</tr>
</tbody>
</table>

**Hypertension:** Hypertension is one of the major toxicities that may be experienced with bevacizumab. The first 6 patients must have blood pressure measured and recorded daily during the first 6 weeks then three times weekly along with all other patients accrued following the initial six patients.

<table>
<thead>
<tr>
<th>Hypertension*</th>
<th>[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Consider increased BP monitoring</td>
</tr>
<tr>
<td>Grade 2 asymptomatic <strong>but</strong> diastolic BP &lt; 100 mmHg</td>
<td>Begin anti-hypertensive therapy and continue bevacizumab</td>
</tr>
<tr>
<td>-Grade 2-3 Symptomatic <strong>OR</strong> -Diastolic BP &gt; 100 mmHg</td>
<td>• Hold bevacizumab should until symptoms resolve <strong>AND</strong> BP &lt; 160/90mmHg</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue bevacizumab.</td>
</tr>
</tbody>
</table>

The presence of hypertension and proteinuria would favor the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, more so because angiotensin inhibitors restore nephrin expression. Calcium channel inhibitors may interact with ixabepilone through a cytochrome P-450 pathway and should not be recommended.

**Surgical or periodontal procedures:** If there is a need for a major surgical or serious periodontal procedure, bevacizumab should be held for 4 weeks prior to the procedure and must not be resumed until 4 weeks after the surgical procedure.
Longer delays may be necessary if clinically indicated in order to insure that adequate healing has taken place prior to bevacizumab resumption. Minor oral or periodontal procedures or surgical procedures may be done with no delay at the discretion of the PI.

**Thrombosis**

**Arterial Thrombosis:** Patients will be taken off study in the event of arterial thrombosis. Arterial thrombosis includes CNS ischemia, cardiac ischemia, and any visceral or peripheral artery thrombosis.

**Venous Thrombosis:** For venous thrombosis requiring systemic anticoagulation, the patient may continue with bevacizumab and ixabepilone while on systemic anticoagulation. Low molecular weight heparin will be recommended and preferred to coumadin to avoid drug interaction.

### Arterial Thrombosis
- Cardiac ischemia/infraction
- CNS ischemia (TIA, CVA)
- Any peripheral or visceral arterial ischemia/thrombosis

| Grade 2 (if new or worsened since bevacizumab therapy) | Discontinue bevacizumab.
| Grade 3-4 | Discontinue bevacizumab |

### Venous Thrombosis

**Grade 3 OR Asymptomatic Grade 4**
- Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.
- If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met:
  - The subject must have a stable dose of heparin prior to restarting bevacizumab.
  - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)
  - The subject must not have had hemorrhagic events while on study
- If thromboemboli worsen/recure upon resumption of study therapy, discontinue bevacizumab

**Symptomatic Grade 4**
- Discontinue bevacizumab

**Coagulopathy:** Patients with grade 3-4 coagulopathy must hold bevacizumab until the coagulopathy resolves to grade 1.

**Thrombocytopenia (platelets < 50,000 - grade 3 or greater):** Bevacizumab should be held until platelets are grade 1 or better (> 75,000). If held for more than 3 weeks, discontinue therapy. Thrombocytopenia may also be related to ixabepilone, and dose reductions of ixabepilone also apply (as follows below in the ixabepilone section).

If bevacizumab is terminated due to toxicity, patients can continue on monotherapy with ixabepilone.
3.3.2 Ixabepilone-related toxicities:
Dose adjustments will be made according to the guidelines below, with dose levels defined as follows:

Treatment modifications for hematologic toxicities and delay in start of cycle:
Doses will be modified if the start of a cycle is delayed more than two weeks (in all cycles after the first cycle, the day 1 dose will be administered only when the ANC is greater than 1000/mm³ and the platelet count is above 75,000/mm³). There will be no dose modification for a delay of two weeks or less.

Doses will also be modified based upon the nadir from the previous cycle according to the following guidelines.

- **Dose Adjustments for Hematologic Toxicities**
  - **Toxicity**
    - ANC Count ≤ 500 cells/mm³ for ≥ 4 days
      - **Dose Adjustment**
        - Reduce ixabepilone to 4.5mg/m² level
    - Platelet count ≤ 50,000 cells/mm³
      - **Dose Adjustment**
        - Reduce ixabepilone to 4.5mg/m² level
    - Delay in starting cycle > 2 weeks
      - **Dose Adjustment**
        - Reduce ixabepilone to 4.5mg/m² level

General treatment modifications at the time of re-treatment:
If non-hematologic grade 3 and 4 toxicities occur, treatment with both drugs will be interrupted until the toxicity resolves to grade 2 or less. Subsequently, treatment may be restarted and drug dosing modified according to the guidelines below. However, if toxicity does not resolve to ≤ grade 2 within two weeks, that patient will be removed from treatment. Patients who experience grade 4 non-hematologic toxicities will be individually evaluated with regard to continuation of treatment. These patients should not be restarted on therapy once toxicity resolves unless there is some clear indication of patient benefit in the form of objective tumor response. In these cases, the reason(s) for restarting therapy will be clearly indicated in the case report form, and the medical record, and the risks and potential benefits will be discussed with the patient.

Treatment modifications for non-hematologic toxicities:
Dose modifications for non-hematologic toxicities (other than those directly-related to bevacizumab) will be based upon the toxicity from the previous cycle. All toxicities must resolve to grade 2 or less prior to the initiation of a subsequent cycle.

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>ixabepilone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unchanged</td>
</tr>
<tr>
<td>2</td>
<td>unchanged</td>
</tr>
<tr>
<td>3 Note 1</td>
<td>reduce ixabepilone dose to 4.5mg/m² level.</td>
</tr>
<tr>
<td>4 Note 2</td>
<td>reduce ixabepilone dose to 4.5mg/m² level.</td>
</tr>
</tbody>
</table>

Note 1: If grade 3 fatigue or neuropathy occurs but resolves to grade 2 or less by the start of the next cycle, the dose of ixabepilone will remain unchanged.
Note 2: Patients with grade 4 toxicity will not be re-treated unless the grade 4 toxicity is included in the list that follows, in which case adjustments will be made in accordance with the guidelines listed above.

- Grade IV hypocalcemia with normal ionized calcium
- Grade IV uric acid
- Grade IV hypokalemia that responds to medical intervention
- Grade IV hypomagnesemia that responds to medical intervention
- Grade IV hypophosphatemia that responds to medical intervention
- Grade IV sepsis for which a source was identified and treatment successfully instituted
- Grade IV stomatitis

Note 3: Patients with grade 2 alopecia or nail changes persisting at the initiation of the subsequent cycle: no dose modification will be made.

Any other dose reductions in study treatment that are not described above may be performed at the discretion of the investigator after discussion with the sponsor, provided that criteria for subject withdrawal from study treatment described in Section 4.5 have not been met. Doses reduced for drug-related toxicity should generally not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, intrasubject re-escalation back to the previous dose level may be permitted at the discretion of the investigator after discussion with the sponsor.

3.4. CORRELATIVE STUDIES.

3.4.1 Rationale-general considerations.

In the context of this study, tumor and fluid samples will be collected to evaluate the effects of bevacizumab and ixabepilone. In parallel, imaging studies will be conducted and correlated to the biologic changes associated with the treatment. The main objective of these correlative studies is to identify predictive markers of activity, but also to study the mechanisms involved in the synergy between “anti-angiogenic” agents and cytotoxics.

The schedule of these translational studies is summarized in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>C1/D5</th>
<th>C2/D1</th>
<th>Every two cycles (cycle 4, day 1 etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor biopsy</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Imaging DCE-MRI</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two biopsies have specific translational purposes and are both optional. They will be obtained with the assistance of Interventional Radiology if considered minimal surgical risk. Minimal risk biopsies are those where the tumor is accessible without need for general anesthesia. Every attempt will be made to recruit patients with disease that can be sampled by biopsy.
Blood samples: Whole blood and serum samples will be collected for circulating endothelial cells and proteins analysis and archived for analyses related to angiogenesis and molecular targets analysis.

### 3.4.2. Research Blood Samples

**Protein profiling:** Blood samples (16 ml) will be collected before protocol treatment (T0), cycle 1 day 5, cycle 2 day 1 then every 2 cycles (beginning at cycle 4 day 1) prior to study drug administration and immediately centrifuged. Serum will be stored at -80°C until assay. Quantitative determination of serum VEGF-A and soluble VEGFR2 will be performed using the ELISA method. In addition, erythropoietin level will be determined at the same time as a putative indirect marker of activity. Samples will be processed in the laboratory of Dr. John Smith.

**Tumor Endothelial Markers (TEMs, [53]):** Blood samples (8 ml) will be collected before (T0), cycle 1 day 5, cycle 2 day 1 and then every 2 cycles (beginning at cycle 4 day 1) and immediately centrifuged. Serum will be stored at -80°C until assay. Samples will be processed in the laboratory of Dr. John Smith and Dr. William Doe will receive the serum aliquots labeled with study identifiers from Smith’s lab. Patients’ names will not be included on the serum aliquot labels.

**Circulating endothelial cells (CEL):** Blood samples will be collected in three CPT citrate (blue/black tiger top) (24 ml) before treatment (T0), at day 5, and cycle 2, day 1.

To evaluate the effects of bevacizumab and ixabepilone on circulating endothelial progenitors (CEP) and mature circulating endothelial cells (CEC) tubes of peripheral blood will be collected, processed to collect the mononuclear cell fraction, and analyzed using multiparameter flow cytometry. Cells will be analyzed for forward and side scatter, and a dump channel will be created to exclude cells expressing hematopoietic markers such as CD45. Endothelial cells will be identified using coexpression of markers, such as CD31 and CD146 for mature endothelial cells, and CD31 and CD133 for CEP cells. The cell populations will also be analyzed for viability using scatter profiles and a vital stain, such as Hoechst 33258. Percentages of stained cells will be determined and compared with appropriate negative controls. Multiparameter flow analysis will be performed with a BD LSRII equipped with FlowJo software, using a minimum of 500,000 events per analysis.

**Storage, Tracking, Protocol Completion and Sample Destruction:**

**CEL Tracking:**

These samples will be delivered directly to Dr. Doe’s lab for processing. They will be tracked in a computerized database in the Dr. Doe’s laboratory with patient identifiers including medical record number and date/time of acquisition. This is a secure system that can only be accessed by authorized users in Dr. Doe’s lab lab. A hard copy record of this database will be on file with protocol regulatory binders. Any samples remaining at the completion of processing will be sent to Dr. Smith’s lab for storage as outlined below.

**Protein profiling and TEMs**
These blood samples will be stored in the laboratory of Dr. Smith’s and tracked in a computerized database in Dr. Smith’s laboratory. The freezers are located on site in or near Dr. Smith’s labs on the 3rd of the Cancer Center. They will be tracked with patient identifiers including medical record number and date/time of acquisition. This is a secure system that can only be accessed by authorized users in Dr. Smith’s lab. A hard copy record of this database will be on file with protocol regulatory binders. Samples, and associated data, will be stored permanently unless the patient withdraws consent.

3.4.3 Tumor biopsy samples:
Biopsies will be performed at the following times:
- After consent, prior to treatment on cycle 1,
- At the end of cycle 1, prior to cycle 2 drug administration, (this biopsy is optional).

Patients who choose not to undergo optional biopsies will remain on study and continue to receive treatment.

A maximum of two core biopsy samples will be obtained at each of the two biopsy time points, not less than 18-gauge in diameter and at least 1cm in length will be obtained. Inability to get tissue with a reasonable attempt will not preclude treatment and the patient will remain eligible for all other translational components, including imaging.

Microvessel Density Analysis in Tumor Sample:
Tumor samples will be stained and analyzed for microvessel density (MVD) using standard immunohistochemical assays. Quantification of MVD will be assessed using the method of Weidner et al. [54] using CD31 expression. Sections will then be screened to determine the most vascular area of the tumor (hot spot). Within the hot spot area, the stained microvessels will be counted as a single high-power (x 400) field. In addition, immunohistochemical (IHC) analysis will be performed to determine the level of VEGF and VEGFR-2 and -3, HIF1-a, PDGFR-b, but also VEGF independent pathway (SDF-1, Notch, EphrinB2/EphBa, Ang1/Tie2, Ang2/Tie1-2, TGF-1/ALK1 and -2).

Finally, tumor vessel architecture will be studied on tumor biopsies in order to investigate those morphologic modifications in comparison with dynamic imaging modifications.

These samples will be obtained from the tumor biopsy done prior to cycle 1 treatment. They will be processed in the surgical pathology and tracked according Surgical Pathology SOP.

Drug resistance analysis in Tumor Sample.
Recent in vivo reports have demonstrated the importance of infiltrating CD11+Gr1 myeloid cells in anti-VEGF refractoriness [53]. To study the importance of this observation in humans, the homing of CD11+Gr1 will be evaluated using flow cytometric analysis of infiltrating bone marrow mononuclear cells (BMMNCs) from refractory tumor isolates, compared to sensitive tumors. This sample will be obtained from the optional tumor biopsy done just prior to cycle 2. This will be done in the laboratory of Dr. Doe.

3.4.4 Samples remaining at the Completion of Study:
At the completion of the study, once primary research objectives are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. Broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between laboratories or misplaced by researchers. Dr. Smith’s laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB.

3.4.5. Imaging studies

DCE-MRI: DCE-MRI will be performed during cycle one before day 1 treatment and at day 5 (following ixabepilone infusion) in order to compare early tumor blood flow modifications with conventional imaging parameters and clinical treatment benefit. Patients will undergo DCE-MRI using the following parameters. Conventional T1 and T2 weighted images of the target lesion will be obtained and a T1 map will be generated. This will be followed by a series of 3D gradient echo T1 weighted dynamic sequence which will be acquired before, during and after the administration of 0.1mmol/kg of a gadolinium chelate. Data will be analyzed using a general kinetic model by the Clinical Imaging Processing Service (CIPS) in the Diagnostic Radiology Department. This model generates two parameters $K_{\text{trans}}$ and $k_{\text{ep}}$ (permeability terms) that will be used as continuous outcome variables in the analysis. Vascular fraction may also be assessed. Color maps based on these parameters will also be generated. DCE-MRI will also be performed after every 2 cycles and at the time of progression or off-treatment.

3.4.6 Blood samples for Clinical and Research Purposes:

<table>
<thead>
<tr>
<th>Protein profiling (Smith lab)</th>
<th>Baseline Eligibility</th>
<th>C1D1</th>
<th>C1D5</th>
<th>Weekly</th>
<th>C2</th>
<th>Every cycle</th>
<th>Every 2 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating Endothelial Cells (Doe lab)</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Endothelial Markers (Doe lab)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL Research (ml)</td>
<td>48</td>
<td>24</td>
<td>48</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical labs (CBC, coags, chem. 20 panels)</td>
<td>15</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>(First 6 patients)</td>
<td>(Chem20 1x/wk)</td>
<td>(14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Research and Clinical labs (ml)</td>
<td>15</td>
<td>60</td>
<td>24</td>
<td>6 (14)</td>
<td>60</td>
<td>12</td>
<td>36</td>
</tr>
</tbody>
</table>
### 3.5. STUDY CALENDAR.

<table>
<thead>
<tr>
<th>Study Procedure</th>
<th>Screen</th>
<th>Study Treatment [a]</th>
<th>Follow-Up [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1 (Days 1 - 21)</td>
<td>Cycle 2 Day 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td><strong>Baseline Documentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent and Contraceptive Counseling</td>
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<td>Baseline Signs and Symptoms</td>
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<td>Physical Examination</td>
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<tr>
<td><strong>Laboratory Studies</strong></td>
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<tr>
<td>Hematology [1]</td>
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<td>Blood Chemistry</td>
<td>X X</td>
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<td>Coagulation</td>
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<tr>
<td>Pregnancy Test</td>
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<td>Urinalysis/UPCR</td>
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<td>Electrocardiogram</td>
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<td><strong>Study Treatment</strong></td>
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<td>BEVACIZUMAB (15 mg/kg)</td>
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<td>IXABEPILONE</td>
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<td><strong>Tumor Assessments</strong></td>
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<td>DCE-MRI</td>
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<td><strong>Other Clinical Assessments</strong></td>
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<tr>
<td>Concomitant Medications and Treatments</td>
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<td><strong>Research samples</strong></td>
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<tr>
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<tr>
<td>Research blood samples</td>
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*: within 7 days prior Day 1. [1]: CBC with platelet count will be monitored weekly.
3.6 Concurrent Therapies

Potential Drug Interactions: Ixabepilone may have a minimal potential to alter the metabolic clearance of drugs that are highly metabolized by CYP3A4. When ixabepilone was incubated with human liver microsomes along with compounds specific for the inhibition of individual cytochrome P450s, significant inhibition was observed only with the CYP3A4 inhibitors (troleandomycin and ketoconazole) suggesting that ixabepilone may be a substrate for CYP3A4 in humans. Data also indicate that the main route of metabolism of ixabepilone is through CYP3A4.

Inhibitors of CYP3A4 include but are not limited to the following:
- Antibiotics: clarithromycin, erythromycin, troleandomycin
- Anti-HIV agents: delavirdine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir
- Antifungals: itraconazole, ketoconazole, fluconazole (doses > 200mg/day), voriconazole
- Calcium channel blockers: verapamil, diltiazem
- Miscellaneous: amiodarone

Use of the above-mentioned inhibitors with ixabepilone are prohibited.

Current list of drugs that may have potential CYP3A4 interactions can be found at: [http://medicine.iupui.edu/flockhart/](http://medicine.iupui.edu/flockhart/).

3.7 Surgical Guidelines

Patients are allowed to have minor surgical procedures (i.e. dental work, port placement, superficial derm procedures) during the course of the study. Major surgery will be considered on a case by case basis and the study drugs will be interrupted or the patient may be removed from study depending on the nature of the surgery.

3.8 Radiation Therapy Guidelines

No concurrent radiation therapy will be allowed on study.

3.9 Off treatment Criteria.

1. Progression of disease during treatment on study protocol. Decisions will be made at the time of restaging (restaging planned after the second, fourth and sixth cycles and then every third cycle). However, if clinically indicated, a decision may be made following the first cycle, or at the investigator’s discretion, after obtaining the appropriate staging studies.
2. Treatment discontinuation required per section 3.3.1 or 3.3.2 or when therapy is judged detrimental to the patient’s health.
3. Grade 4 hypersensitivity reaction to drug administration (anaphylaxis).
4. Patient voluntary withdrawal.
5. Discretion of the Principal Investigator.

Unacceptable toxicities that have not resolved at time of “off treatment” must be followed until stabilization or resolution.

3.10 Follow-Up and Off Study Criteria

1. Patients who stop treatment for reasons other than progression will be followed
in order to determine time to progression. Follow-up will be done either in-person or at their local physician’s office with records forwarded to us.
Scans will be obtained at a minimum of 3 month intervals following off treatment,
2. At the time progression is noted, patients will be removed from study.
4. Patients who stop treatment for progression will be removed from study at the same time they are removed from treatment.

4.0. Supportive Care Guidelines

Patients will be allowed continued use of erythropoietin or similar analogs that may have been initiated prior to entry. No concomitant use of alternative, complementary therapies will be allowed without prior approval of the PI.

Patients who have experienced substantial clinical benefit in the form of tumor reduction resulting in manageable, but increased toxicity that would otherwise require cessation of therapy, will be allowed to continue on therapy at the discretion of the associate investigator physician or PI, after approval by sponsors and the IRB as described in section 5. The patients will remain officially on study and their responses will be analyzed as such. Management of toxicities that are likely relating to the investigational agents are found in section 3.3.

5.0 Data Collection and Evaluation

5.1 Data Collection:

All of the patients who enroll on study will be included in the main analysis. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Data will be prospectively collected and entered into the Cancer Center’s database. Complete records must be maintained on each patient participating in this trial and retained for at least two years following the notification date of IND closure.

All patients included in this study must be assessed for response to treatment every 2 cycles. Each patient will be assigned one of the following categories: 1) complete response; 2) partial response; 3) stable disease; 4) progressive disease; and 5) not evaluable (early death from malignant disease, early death from toxicity, early death due to other causes, or unknown-not assessable, insufficient data).

5.2 Response Criteria

For the purposes of this study, patients should be reevaluated for response every 2 cycles (6 weeks). In addition to a baseline scan, confirmatory scans should also be 4 weeks following initial documentation of objective response.

5.2.1 Definitions

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

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

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

### 5.2.2 Guidelines for Evaluation of Measurable Disease

**Disease Parameters**

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

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

**Non-measurable disease.** All other lesions (or sites of disease), including small lesions (longest diameter $<10$ mm or pathological lymph nodes with $\geq 10$ 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.

**Methods for Evaluation of Measurable Disease**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 5.2.3 Evaluation of Response

#### 5.2.3.1 Evaluation of Target Lesions

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

**Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

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

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

### 5.2.3.2 Evaluation of Non-Target Lesions

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

### 5.2.3.3 Evaluation of Best Overall Response

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

**For Patients with Measurable Disease (i.e., Target Disease)**
### 5.2.4 Duration of Response

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

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

**Duration of stable disease:** Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the

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<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
<th>Best Overall Response when Confirmation is Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>&gt;4 wks. Confirmation**</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
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<td>PR</td>
<td>&gt;4 wks. Confirmation**</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-CR/Non-PD/ not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-CR/Non-PD/ not evaluated</td>
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<td>SD</td>
<td>documented at least once &gt;4 wks. from baseline**</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>PD***</td>
<td>Yes or No</td>
<td>PD</td>
<td>no prior SD, PR or CR</td>
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*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.

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

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
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<tr>
<td>Not evaluated</td>
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<tr>
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<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*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.
smallest measurements recorded since the treatment started, including the baseline measurements.

5.2.5 Progression-Free Survival

Progressions-Free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

5.3 Toxicity Criteria

The descriptions and grading scales found in the active version of the Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for adverse event reporting. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

5.4 Statistical Methods

STATISTICAL CONSIDERATIONS.

The primary objective of this study is to determine if the objective response rate (CR + PR) of the combination of bevacizumab and ixabepilone is sufficiently high to warrant further evaluation in patients with mRCC. Secondary objectives include description of progression free survival, toxicity, as well as evaluation of a variety of surrogate markers to determine if treatment impacts these parameters, and to see if the changes may be associated with clinical outcome. These studies will include characterization of effects on angiogenic signaling cascades, imaging studies or molecular and cellular events involved in drug resistance.

Limited activity of second line antiangiogenic therapy has been reported after anti-VEGF or VEGFR inhibitors failure, with a response rate ranging from 10 to 23% for single agents. In order to establish if the combination of bevacizumab and ixabepilone is able to be associated with a response rate which is likely to exceed that of either agent alone, a Simon two-stage MiniMax design will be used to determine whether the addition of ixabepilone to bevacizumab is able to rule out a 20% response rate (p0=0.20) and to target a more desirable 35% response rate (p1=0.35). Using alpha=0.10 and beta=0.10, initially 33 evaluable patients will be enrolled and receive treatment. If there are 0-6 clinical responses in these 33 patients, then no further patients will be enrolled. If there are 7 or more clinical responses in these patients, then accrual will continue until a total of 58 evaluable patients have been enrolled and treated. If needed, patient accrual may be paused temporarily after the first stage to ensure that sufficient responses have been identified to warrant accrual to the second stage. If there are 7 to 15 clinical responses, this will be considered inadequate for further consideration, while if 16 or more patients experience a clinical response from among 58 patients, then this combination will be considered worthwhile for further investigation in this patient population. Under the null hypothesis (20% clinical response rate), the probability of early termination is 50%.
A variety of markers will be evaluated at baseline as well as at cycle 2, day 1 of treatment. Changes from baseline will be determined in either absolute or relative terms as appropriate, and evaluated for statistical significance, as well as to determine if the changes or the actual values at a time point are associated with clinical response. Paired comparisons with baseline will be done using a paired t-test or Wilcoxon signed rank test as appropriate, and, if accrual is able to continue onto the second stage, the changes will be compared between responders (CR + PR) and non-responders (SD + PD) using a two sample t-test or Wilcoxon rank sum test as appropriate. As an example, if 10 markers were evaluated compared to baseline, and if 20 patients had paired data, there would be 88% power to declare a given marker change from baseline to be significant at the 0.05 level after adjusting for multiple comparisons by the Bonferroni procedure, although less stringent adjustments may be made in practice as these would be secondary endpoints.

MRI parameters will also be obtained at the same time points, and changes in these parameters will also be compared in a similar fashion, both with respect to the changes themselves, and with respect to any association with clinical response.

In all such cases, these analyses will be considered exploratory and not formally adjusted for multiple comparisons. However, to ensure proper interpretation in the context of a potentially large number of explorations being performed, only p-values <0.01 will be interpretable as being associated with statistical significance.

Kaplan-Meier curves depicting time to progression on ixabepilone + bevacizumab will be created, and appropriate 95% confidence intervals will be presented.

The worst grade of toxicity of a given type for each patient will be tabulated, the frequency of grade 3 or greater toxicities will be calculated, and appropriate 95% confidence intervals will be formed.

It is anticipated that 30 patients per year may enroll onto this trial. Thus, it is expected that 2 years may be required to complete patient accrual. In order to allow for the possibility of a very small number of inevaluable patients, the accrual ceiling will be set at 60 patients.

5.5 Multi-Institutional Guidelines
This is a single institution study

5.6 Data and Safety Monitoring Plan

Monitoring of this protocol will consist of continuous, close monitoring by the Principal Investigator, with prompt reporting of serious adverse events to the IRB and the Sponsor. The Principal Investigator will monitor the trial with the assistance of the Associate Investigators including the Research Nurse(s). In the event that any severe or unexpected side effects are noted, these will be reported to the IRB and Sponsor. This approach will ensure that adverse event reporting requirements are met. In addition,
data will be examined weekly at a Protocol Review Meeting, usually conducted on the day of clinic. These meetings will assess the progress of the protocol and discuss any side effects observed, including both expected and unexpected side effects. At this time the accuracy of the accrued data is verified.

A summary of the ongoing study will be submitted to the Institutional Review Board at 12 month intervals and a final report will be sent within six months of study completion at the request of the Institutional Review Board.

6.0. HUMAN SUBJECT PROTECTIONS

6.1 Rationale for Subject Selection:
This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, only pregnant women and children are excluded from this study. This study will be recruited through internal referral, our local physician referral base, and through various cancer information hotlines (i.e., 1-800-4Cancer). All individuals with RCC (clear cell) that is refractory to VEGFR inhibitors are eligible according to the eligibility criteria within section 3. This is a Phase II trial designed to determine response, further characterize the side effect profile, and assess several biological and imaging endpoints. Because this is a phase II study, clinical benefit may be possible. Patients should realize that we are hopeful that they may gain benefit from this study, but there is no objective evidence to support our optimism at this time. Patients must have failed standard first-line therapy of proven efficacy for their disease. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in section 3. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

6.2 Participation of Children:
Patients under the age of 18 will be excluded from study.

6.3 Evaluation of Benefits and Risks/Discomforts:
The potential benefit to a patient who enters study is a reduction in the bulk of their tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

6.4 Risks/Benefits Analysis:
6.4.1 Potential Risks
6.4.1.1 Risk of serial biopsies: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks
(such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the Cancer Center. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

6.4.1.2 Risk of Treatment: Details of the risk of drug therapy are detailed in section 6.

6.4.1.3 Risks of radiation exposure: This study incorporates serial imaging with CT scans for biopsy guidance (where needed) in the second part of the study.

6.5 Consent and Assent Process and Documentation:
An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. Original consents will be placed in the Medical Record. Copy placed in research record.

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

7.0 DATA REPORTING

7.1 IRB Expedited Adverse Event Reporting Criteria
The protocol PI will report to the IRB with:
- All serious adverse events (SAEs) that are not in the consent form, but are possibly, probably, or definitely related to the research. An SAE is defined as an untoward medical occurrence that:
  o Resulted in a death;
  o Was life-threatening;
  o Required or prolonged hospitalization;
  o Caused persistent or significant disability/incapacity;
  o Resulted in congenital anomalies or birth defects; or
  o Required intervention to prevent permanent impairment or death.
- All other deaths that occur that are expected and not related to the research.
- All deaths that occur within 30 days of the last dose of study drug or treatment.
- All Grade 3 and 4 (CTCAE) events that are not in the consent and that are possibly, probably, or definitely related to the research,

Reports must be received by the IRB via the IRB database within 7 days of PI notification of the event.
7.2 IRB Requirements for PI Reporting of Expected and Unexpected Adverse Events at Continuing Review

The IRB requires a summary report of adverse events that have occurred on the protocol since the previous continuing review. The method of presentation should provide the IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination. The summary report is based on the following guidance:

Any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.

In addition, the protocol PI will report to the IRB:

- All Grade 2 events that are not in the consent form, but 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.

7.3 Sponsor Expedited Adverse Event Reporting Requirements

All Serious Adverse Events will be reported by the PI or designee to the pharmacovigilence department at Drug Company of America, Inc within 48 hours of the PI being notified of the event. The SAE report form (found in the study manual) will be completed and faxed to 1-800-555-8989.

Expedited Adverse Event Reporting Exclusions

Grade 3 or 4 myelosuppression, whether or not hospitalized, will not require expedited reporting.

7.4 Sponsor Routine Adverse Event Reporting:

Adverse events will be reported to the sponsor via data transfer from the Cancer Center’s database to the Sponsor’s database on a monthly basis, in addition to the expedited reporting described above.

8. PHARMACEUTICAL INFORMATION.

8.1 Bevacizumab

Other Names: rhuMAb VEGF, Avastin®

Classification: Recombinant humanized monoclonal antibody
**Molecular Weight:** Approximate molecular weight is 149,000 daltons

**Mode of Action:** Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

**Description:** Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions.

**How Supplied:** Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

**Preparation:** Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

**Storage:** Upon receipt, refrigerate bevacizumab (2°C to 8°C). Do not freeze. Do not shake.

**Stability:** Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry. Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours.

**Route of Administration:** Intravenous

**Method of Administration:** Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

1. When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing. Please note: the flush is not included in the total recommended infusion times.

**8.1.1 Adverse Events:**
The following is a description of major adverse events associated with bevacizumab therapy. For additional events refer to the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

**Infusion-Related Reactions:** Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

**Hypertension:** Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% (all grade) across trials, with a mean increase of +5.5mmHg to +8.4mmHg for systolic pressure, or +4.1mmHg to +5.4mmHg for diastolic pressure. Incidence of grade 3 (hypertension requiring initiation of or increase in hypertensive medications) ranges from 7.8 to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of bevacizumab-treated patients.

Hypertension associated with bevacizumab can generally be controlled with routine oral drugs while bevacizumab is continued. However, incidents of hypertensive crisis with encephalopathy (including RPLS – reversible posterior leukoencephalopathy syndrome – see below) or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with standard medical practice (Chobanian et al, 2003). Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

**Proteinuria:** Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from mild asymptomatic increase in urine protein (incidence of about 38%) to rare instances of grade 3 proteinuria (> 3.5gm/24 hour urine) (3%) or nephrotic syndrome (1.4%). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. The risk of proteinuria may be higher in patients with advanced RCC or history of hypertension. There is also evidence from dose-finding trials that the rate of proteinuria may be dose related.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 3 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

**Hemorrhage:** Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

**Tumor-associated hemorrhage** - Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in patients with NSCLC. In a phase 2 study in NSCLC, 6 cases of life-threatening (4 fatal) hemoptysis were reported among 66 patients treated with bevacizumab and chemotherapy (Novotny et al., 2001); squamous cell histology was identified as the risk factor. In the phase III trial in non-squamous NSCLC (E4599), the rate of Grade ≥ 3 pulmonary hemorrhage was <1% in the control arm (carboplatin/paclitaxel) versus 2.3% in the chemotherapy plus
bevacizumab arm (10/427 patients, including 7 deaths). [To be added for protocols involving NSCLC: Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.]

Gastrointestinal hemorrhages, including rectal bleeding and melaena have been reported in patients with colorectal cancer, and have been assessed as tumor-associated hemorrhages. In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL.

Serious tumor associated bleedings have also been observed in patients with pancreatic cancer, gastric cancer, CNS metastases, hepatoma or varices treated with bevacizumab.

**Mucocutaneous hemorrhage** - Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

**Arterial Thromboembolic Events (ATE):** The risk of arterial thromboembolic events is increased with bevacizumab therapy; such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction (MI) and other peripheral or visceral arterial thrombosis. A pooled analysis of five randomized studies showed a two-fold increase in these events (3.8% vs. 1.7%). ATE led to a fatal outcome in 0.8% patients with bevacizumab (vs. 0.5% without bevacizumab). The rate of cerebrovascular accidents (including TIA) was 2.3% vs. 0.5%, and the rates of MI 1.7% vs. 0.7%. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Skillings et al., 2005). In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of ATE was approximately 8.5%.

Aspirin is a standard therapy for primary and secondary prophylaxis of ATE in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATE events, retrospective analyses of the ability of aspirin to affect the risk of ATE were inconclusive. Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

**Venous thromboembolism (VTE) (including deep venous thrombosis, pulmonary embolism and thrombophlebitis)** – In the Phase III pivotal trial in metastatic CRC, there was a slightly higher rate of VTE in patients treated with chemotherapy + bevacizumab compared with chemotherapy alone (19% vs. 16%).
The incidence of NCI-CTC Grade ≥ 3 VTEs in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%).

In clinical trials across all indications the overall incidence of VTEs ranged from 2.8% to 17.3% in the bevacizumab-containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE compared with chemotherapy alone. However, patients with mCRC who receive bevacizumab and experienced VTE may be at higher risk for recurrence of VTE.

**Gastrointestinal Perforation:** GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in non-CRC tumors (e.g. gastric/esophageal, pancreatic and ovarian cancers) or nonmalignant conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

**Fistula:** Fistula formations, including events resulting in death, have been observed in patients receiving bevacizumab in clinical studies and post-marketing reports. Fistulae in the GI tract are common (1-10% incidence) in patients with certain metastatic tumors such as colorectal cancer or cervical, but uncommon (0.1-1%) or rare (0.01-0.1%) in other indications.

In addition, fistulae that involve areas other than the GI tract have also been observed (e.g. tracheoesophageal, bronchopleural, urogenital, biliary). Events were reported at various timepoints during treatment, ranging from 1 week to >1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

**Information to be included in trials with bevacizumab in combination with chemoradiation for thoracic tumors:** Life-threatening or fatal tracheoesophageal fistula has been reported in patients with small cell lung cancer treated with concurrent chemoradiation and bevacizumab. In a phase II trial of irinotecan + carboplatin + RT and bevacizumab followed by maintenance bevacizumab that accrued 25 patients, there have been two confirmed cases of tracheoesophageal (TE) fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of chemoradiation). While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without radiation), the incidence was extremely low.

**Wound Healing Complications:** Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab.
The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. Across metastatic CRC trials, at least 28 days must have elapsed following major surgery before bevacizumab could be initiated; data suggested initiation of bevacizumab 29-60 days following surgery did not appear to increase the risk of wound healing complications compared to those treated with chemotherapy alone.

The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined. In the pivotal study in CRC, among patients who underwent major surgery while on study therapy, there was an increased rate of significant post-operative bleeding or wound healing complications in the IFL + bevacizumab arms vs. IFL alone [10% (4/40) vs. 0% (0/25)] (Scappaticci 2005). Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, range 11-50 days).

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

**Congestive Heart Failure (CHF):** The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, CHF or cardiomyopathy were reported in 3% in the bevacizumab+capecitabine arm compared to 1% in the capecitabine-only arm (Miller et al. 2005). In a Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm.

In phase II study of 48 patients with refractory acute myelogenous leukemia treated with cytarabine, mitoxantrone, and bevacizumab, 5 cases of cardiac dysfunction (CHF or decreases to <40% in left ventricular ejection fraction, including AML trial); were reported. All but one of these subjects had significant prior exposure to anthracyclines as well.

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin (cumulative doses at 240 mg/m2), and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40% (Wedam et al. 2004). In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m²) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m², one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m²); an additional 4 patients had asymptomatic decreases in LVEF (D'Adamo et al. 2004).

Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES) or similar leukoencephalopathy syndrome:

RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, visual disturbance or cortical blindness, with or without associated hypertension. MRI scans are required for diagnosis. [Typical findings are vasogenic edema (enhanced intensity in T2 and FLAIR sequences on non-contrast MRI) predominantly in the white matter of the posterior parietal and occipital lobes, and less frequently, in the anterior distributions and the gray matter].

RPLS/PRES is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

Neutropenia: In the phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% with bevacizumab + IFL vs. 14% with IFL (grade 4 neutropenia was 3% vs. 2%). Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab. In a phase 3 in NSCLC, carboplatin and paclitaxel + bevacizumab arm was associated with increased rate of grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and infection with neutropenia (4.4% vs. 2.0%) with three fatal cases (Sandler et al. 2006).

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, ranging from 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.
8.2 IXABEPILONE (BMS-247550; Ixempra®):

Chemical Name: \((1S,3S,7S,10R,11S,12S,16R)-7,11\text{-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.}\)

Other Names: Epothilone B analog, Ixabepilone, Ixempra®

Molecular Formula: \(\text{C}_{27}\text{H}_{42}\text{N}_{2}\text{O}_{5}\text{S}\)  M.W.: 506.7 grams/mole

Mode of Action: BMS-247550 is a semi-synthetic analog of the natural product epothilone B. The epothilones are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of cellulose degrading myxobacteria, Sorangium cellulosum.

Description: Epothilone B analog

How Supplied: BMS-247550 appears as a lyophilized, white to off-white color, whole or fragmented cake in a vial. The drug product is available in 15 mg and 45 mg vials.

<table>
<thead>
<tr>
<th>BMS-247550 vial size</th>
<th>Diluent provided</th>
<th>Volume of diluent needed for reconstitution of drug vial</th>
<th>Final concentration</th>
<th>Actual Amount of Drug in Vial**</th>
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</thead>
<tbody>
<tr>
<td>15 mg</td>
<td>8 mL vial</td>
<td>8 mL</td>
<td>2 mg/mL</td>
<td>16 mg</td>
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<tr>
<td>45 mg</td>
<td>23.5 mL vial</td>
<td>23.5 mL</td>
<td>2 mg/mL</td>
<td>47 mg</td>
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**To account for vial/needle/syringe loss, the actual amount of drug in the vial differs from the amount of drug on the product label.

The Vehicle for Constitution of BMS-247550 for injection (diluent) appears clear to slightly hazy and is colorless to pale in color. The diluent is an ethanol plus polyoxyethylated castor oil (Cremophor® EL) mixture (1:1 by volume).

Reconstitute the drug vial with the provided diluent only. Diluents are not interchangeable and should only be utilized to reconstitute a particular strength.

Preparation: Prior to constitution of the lyophile, bring the lyophile and diluent vial to room temperature for approximately 30 minutes. (If the diluent is stored in the refrigerator, a white precipitate may appear when it is first removed. The precipitate will disappear once the vehicle reaches room temperature.) Slowly inject 8 mL or 23.5 mL of the diluent into the 15 mg vial or 45 mg vial, respectively. Gently swirl the vial until the lyophile is dissolved completely. This results in a 2mg/mL solution. Further dilute with Lactated Ringer's Injection (LRI) to a final BMS-247550 concentration of 0.2 mg/mL to 0.6 mg/mL in a non-PVC container before administration to the patient. (Please note: BMS-247550 concentrations below 0.2 mg/mL are no longer recommended.)

Storage: Store BMS-247550 for Injection in the refrigerator (2° to 8°C) prior to use and protect from light.

Store the Vehicle for Constitution in the refrigerator or at room temperature (2°C to 25°C).
**Stability:** Shelf life surveillance is ongoing. After initial *constitution* with the accompanying diluent, the product may be stored for a maximum of one (1) hour at room temperature and room light. *After final dilution in Lactated Ringers for Injection (LRI) to concentrations between 0.2 and 0.6 mg/mL, the drug product is stable at room temperature and light for a maximum of 6 hours.*

**Route of Administration:** Administer the BMS-247550 infusion intravenously through an appropriate in-line filter with a microporous membrane of 0.22 to 5 microns. Flush the IV line or extension set with LRI at the end of the infusion, if flushing is required.

**Incompatibilities:** Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di-(2-ethylhexyl)phthalate (DEHP) to prevent DEHP leaching into the infusion medium. Store diluted BMS-247550 solutions in bottles (glass, polypropylene) or plastic bags (polyethylene, polypropylene, polyolefin, ethylene-vinyl-acetate) and administer through polyethylene-lined administration sets or PVC sets plasticized with TOTM (trioctyl trimellitate). IV sets and components typically used for the administration of paclitaxel are compatible with BMS-247550 infusions.

1. **Potential Drug Interactions:** The following strong inhibitors of CYP3A4 are prohibited: ketoconazole, itraconazole, ritonavir, amprenavir indinavir, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, nelfinavir, delavirdine, and voriconazole.
   If there are no other treatment options other than the above named drugs, consultation with the PI is mandatory and each patient’s situation will be reviewed on a case by case basis with final decision made by the PI.
2. Use caution when considering the use of other CYP3A4 inhibitors with BMS-247550. Co-administration of BMS-247550 with CYP3A4 inducers may decrease its plasma concentrations and therapeutic effects.

   *In vitro*, BMS-247550’s weak inhibition of human CYP3A4 suggests that it may have a minimal potential to alter the metabolic clearance of drugs metabolized by CYP3A4.

A more complete list of CYP3A4 inhibitors is found in Appendix C and should be consulted when making decisions regarding concurrent therapies.

**Drug ordering and accountability:** Drug may be requested by completing a Drug Request Form (found in study reference manual) and faxing to.

**Precautions/overdose:** BMS-247550 is an investigational agent and is contraindicated for all conditions other than those mentioned in the protocol and the Investigator Brochure.

**Disposition of study medications:** Any remaining solution should be discarded according to institutional procedures for cytotoxics. At the end of the study all unused stock will be returned to CTEP who will arrange for its disposition.
### 8.2.1 Adverse Events:

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;20%)</th>
<th>Rare but Serious (&lt;3%)</th>
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<tbody>
<tr>
<td><strong>ALLERGY/IMMUNOLOGY</strong></td>
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<td>Allergic reaction/hypersensitivity (including drug fever)</td>
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<td><strong>BLOOD/BONE MARROW</strong></td>
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<td>Hemoglobin</td>
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<td>Leukocytes (total WBC)</td>
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<td>Lymphopenia</td>
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<td>Neutrophils/granulocytes (ANC/AGC)</td>
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<td>Platelets</td>
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<td><strong>CARDIAC ARRHYTHMIA</strong></td>
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<td>Sinus bradycardia</td>
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<td><strong>CARDIAC GENERAL</strong></td>
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<td>Cardiac ischemia/infarction</td>
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<td>Cardiac troponin T (cTnT)</td>
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<td>Hypotension</td>
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<td><strong>COAGULATION</strong></td>
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<td>INR (International normalized ratio of prothrombin time) in patients on Coumadin</td>
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<td><strong>CONSTITUTIONAL SYMPTOMS</strong></td>
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<td>Fatigue</td>
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<td>Fever</td>
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<td>Insomnia</td>
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<td>Weight loss</td>
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<td><strong>DERMATOLOGY/SKIN</strong></td>
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<tr>
<td></td>
<td>Flushing</td>
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<td>Hair loss/alopecia (scalp or body)</td>
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<td></td>
<td>Injection site reaction/extravasation changes</td>
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<td>Nail changes</td>
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<td>Pruritus/itching</td>
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<td>Rash: dermatitis associated with radiation: Chemoradiation</td>
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<td>Rash/desquamation</td>
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<td>Rash: hand-foot skin reaction</td>
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<td><strong>GASTROINTESTINAL</strong></td>
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<td>Anorexia</td>
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<td>Dysphagia (difficulty swallowing)</td>
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<td>Heartburn/dyspepsia</td>
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<td>Pulmonary/Upper Respiratory</td>
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<td>Dyspnea (shortness of breath)</td>
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<td>Hiccoughs (hiccups, singultus)</td>
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<td>Vascular</td>
<td>Acute vascular leak syndrome</td>
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**Note:** BMS-247550 (ixabepilone) 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.
8.3 DIPHENHYDRAMINE HYDROCHLORIDE (HCl) INJECTION:

8.3.1 General issues: Diphenhydramine hydrochloride (Benadryl) is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N, N-dimethyl-ethylamine hydrochloride. It occurs as a white, crystalline powder, is freely soluble in water and alcohol and has a molecular weight of 291.82. The molecular formula is C_{17}H_{21}NO·HCl.

8.3.2. Other pharmaceutical issues:

Supply: Commercially available.

Product description: Diphenhydramine HCl injection is available in an injectable solution at a 50 mg/ml concentration in single dose ampoules, syringes and vials as well as multi-dose vials from multiple manufacturers.

Solution Preparation: Diphenhydramine HCl may be given by direct intravenous injection without additional dilution. Alternatively the prescribed dose may be diluted in a small volume (e.g. 25 - 50 ml) of 5% dextrose in water (D5W) or 0.9% sodium chloride (NS) and infused over 10 - 15 minutes.

Storage: Store commercially available injectable product at controlled room temperature.

Route of Administration: Diphenhydramine HCl injection may be administered by direct IV injection (IV push) at a rate generally not exceeding 25 mg/min. Alternatively, diphenhydramine HCl injection may be diluted and given over 10 - 15 minutes (see solution preparation).

Toxicities: Sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, thickening of bronchial secretions. Diphenhydramine can produce additive effects with alcohol or other CNS depressants. Diphenhydramine can cause anticholinergic side effects (e.g. dry mouth, fixed or dilated pupils, flushing, urinary retention). Diphenhydramine should be used with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.

PLEASE REFER TO THE PACKAGE INSERT FOR FURTHER INFORMATION.

8.4. RANITIDINE HYDROCHLORIDE (HCI) INJECTION:

8.4.1. General issues: Ranitidine hydrochloride (HCl) (the active ingredient in Zantac Injection and Zantac Injection Premixed) is a histamine H_{2} -receptor antagonist. Chemically it is N’-[2-[5-[(dimethylamino)methyl]-2-furanylmethyl][thio]ethyl]-N’- methyl-2-nitro-1,1-ethenediamine, hydrochloride. The empirical formula is C_{13}H_{22}N_{4}O_{3}S·HCl, representing a molecular weight of 350.87.

8.4.2. Other pharmaceutical issues:

Supply: Commercially available.
**Product Description:** Ranitidine HCl injection is available in an injectable solution at a 25mg/ml concentration in 2, 10 and 40 ml vials and in a 2 ml syringe. It is also available in a single dose pre-mixed 50 mg parenteral bag in 50 ml of 0.45% sodium chloride (1/2NS). Ranitidine HCl is manufactured by Glaxo Wellcome Inc. under the trade name Zantac.

**Solution preparation:** For direct intravenous injection, dilute prescribed dose with a compatible diluent [e.g. 5% dextrose in water (D5W), 0.9% sodium chloride (NS) or lactated ringers (LR)] to a total volume of 20 ml prior to injection. For intermittent intravenous infusion, dilute prescribed dose in 25 – 100ml of a compatible diluent (e.g. D5W, NS or LR). Once diluted in a compatible diluent, ranitidine is stable for 48 hours at room temperature and 4 days refrigerated.

**Storage:** Ranitidine HCl injection should be stored between 4°C and 30°C and protected from light and excessive heat. The premixed infusion solution should be stored between 2°C and 25°C.

**Route of administration:** Ranitidine HCl may be administered by direct intravenous injection or infusion. For direct intravenous injection, dilute prescribed dose to a volume of 20 ml with a compatible diluent and inject over a period of not less than 5 minutes. For intermittent intravenous infusion, infuse prescribed dose over 15 - 20 minutes.

**Toxicities:** Headache, reversible confusional states (e.g. mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), increased transaminase levels, increased serum creatinine, rash, allergic reactions, and hematologic toxicity (e.g. leucopenia, thrombocytopenia, pancytopenia).

PLEASE REFER TO THE PACKAGE INSERT FOR FURTHER INFORMATION.
9. REFERENCES


APPENDIX A

Daily Blood Pressure Log

Patient name ___________________ Patient medical record number __________________
Cycle ___ Start date ___________

Home Blood Pressure Log

This form is to be completed by the participant. Please monitor your blood pressure every day during the first two cycles. Take readings at least 30 minutes after waking and either before or at least an hour after meals. Rest while seated with the arm supported at heart level for at least 5 minutes, then take three readings, separated by ≥ 30 seconds.

*If there is a difference of more than 10mm Hg (systolic or diastolic) between the second and third readings in one sitting record a fourth and fifth reading for that sitting in the column on the right.

Arm Used:  □ Left  □ Right

<table>
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<th>Time</th>
<th>Systolic</th>
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<th>Heart Rate</th>
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### Three times a week Blood Pressure Log

Patient name _________________  Patient medical record number ________________
Cycle ___  Start date ____________

**Home Blood Pressure Log**

This form is to be completed by the participant. Please monitor your blood pressure *three times a week*. Take readings at least 30 minutes after waking and either before or at least an hour after meals. Rest while seated with the arm supported at heart level for at least 5 minutes, then take three readings, separated by ≥ 30 seconds.

*If there is a difference of more than 10mm Hg (systolic or diastolic) between the second and third readings in one sitting record a fourth and fifth reading for that sitting in the column on the right.

**Arm Used:** □ Left  □ Right

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