Amendment

Protocol Number: 09C0057-N **Reference Number:** 350588

Principal Investigator: Ravi Madan NCI GMB 301.496.3493 madanr@mail.nih.gov

(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: A Phase II Multi-Center Study of Bevacizumab in Combination with Ixabepilone in Subjects with Advanced Renal Cell Carcinoma

SIGNATURES

Principal Investigator (*):
Tito Fojo - applied signature on 08/10/2015 1:22 PM EDT
Ravi Madan - applied signature on 08/10/2015 11:46 AM EDT

Accountable Investigator:
William Dahut - applied signature on 08/10/2015 11:47 AM EDT

Branch Chief/CC Department Head (**):
James L Gulley, MD PhD - applied signature on 08/10/2015 4:23 PM EDT

Medical Advisory Investigator (if applicable):
N/A

Lead Associate Investigator signature:
N/A

Referral Contact signatures:
N/A

Associate Investigators signatures:
N/A

For Institute/Center Scientific Review Committee:
N/A

Other IC Clinical Director signatures:
N/A

APPROVALS

IRB Chair:
Michael Hamilton - applied signature on 08/13/2015 8:35 AM EDT

Clinical Director:
Kevin Camphausen - applied signature on 08/13/2015 7:59 AM EDT

CONCURRENCE

OPS Protocol Specialist:

Aruna Acharyya	AM N	08/18/2015
Signature	Print Name	Date

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

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

IRB Meeting Date: Expedited

DEC Clearance Date: 08/05/2015

Protocol Version Date: 07/28/2015

Abbreviated Title: Beva & Ixa in RCC
NCI Protocol #: 09-C-0057 N
CTEP #: 8277
Version Date: 07/28/2015

Title: A Phase II Multi-Center Study of Bevacizumab in Combination with Ixabepilone in Subjects with Advanced Renal Cell Carcinoma.

Principal Investigator:

Ravi Madan, M.D., GMB/CCR/NCI
Bldg 10, Room 3-4460
10 Center Drive
Bethesda, MD 20892 -2279
Phone: 301- 496-3493
FAX:-301- 480-5094
Email: madanr@mail.nih.gov

Research Nurse:

Maureen Edgerly, R.N., OCD/CCR/NCI

Associate Investigators:

Margarita Velarde, CFNP, GMB/CCR/NCI
Peter Choyke, M.D.,MIP/CCR/NCI
Karen Kurdziel, M.D., MIP/CCR/NCI
Jane Trepel, DTB/CCR/NCI
Sanjeeve Balasubramaniam, M.D., FDA
Maria Merino, M.D., Pathology/CCR/NCI
Seth Steinberg, Ph.D., BDMS/CCR/NCI
Tito Fojo, M.D., Ph.D., Columbia University

Brad St Croix, Ph.D.
Tumor Angiogenesis Section
Mouse Cancer Genetics Program
National Cancer Institute - Frederick
PO Box B, Building 560
1050 Boyles Street
Frederick, MD 21702-1201

Study Sponsor: CTEP
IND #: Agent name: 59699 (BMS-247550; Ixempra®)
7921 (Bevacizumab, Avastin®)

Participating Site Information:

This protocol includes the participation of affiliate investigators to administer some portions of the patient's treatment as authorized by the Principal Investigator and approved by the Cancer Therapy Evaluation Program. The Principal Investigator will make all treatment decisions

related to the protocol and these will be conveyed by the Protocol Chair to the affiliated investigators. The Principal Investigator is responsible for the research data and for the appropriate use of the study agent. Affiliate investigators have obtained IRB approval to participate in this CTEP-sponsored trial.

Medical University of South Carolina:

Institutional PI: Harry Drabkin, MD
Institution: Medical University of South Carolina
Institution FWA# 1888
Address: 96 Jonathan Lucas St. Rm 903 CSB, Charleston SC 29425
Phone Number: 843-792-4271
Email: Drabkin@musc.edu
Fax: 843-876-1963

IRB Contact: Summer Young
IRB of Record Name: Office of Research Integrity
Address: 19 Hagood Ave. Suite 701K, Charleston SC 29425
Phone Number: 843-792-4148
Email: youngsn@musc.edu
Fax: 843-792-7457

Pharmacy Contact: Jason Mills, PharmD
Address: 169 Ashley Ave., Room 161 MUSC Hospital, Charleston SC 29425
Phone Number: 843-792-9643
Email: millsja@musc.edu
Fax: 843-792-2834

Study Coordinator: Seth Price
Address: 86 Jonathan Lucas St. Rm 373, Charleston SC 29425
Phone Number: 843-792-1918
Email: pricesr@musc.edu
Fax: 843-876-1963

PRECIS

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 Objectives:

- 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.

Eligibility:

- Pathologic confirmation of renal cell carcinoma (clear cell histology) by the Laboratory of Pathology, NCI, or the Medical University of South Carolina.
- Presence of metastatic renal carcinoma, after progression or intolerance to VEGFR inhibitors (sunitinib and/or sorafenib).
- Adequate organ and bone marrow function.

Design:

- Multi-center, open labeled phase II study
- Following a Simon two-stage optimal design, a maximum of 58 patients with metastatic RCC will be accrued.
- 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 +/- 5 days). Following cycle 6, cycles will be spread out to 4 weeks or 28 days +/- 5 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.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 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).

1.1.2 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.

1.2 BACKGROUND AND RATIONALE

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 IgG_1, 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 ≥ 1mg/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 clinical trial conducted by Hurwitz et al [7], the addition of bevacizumab- to fluorouracil-based combination chemotherapy (irinotecan, bolus fluorouracil, and leucovorin [IFL]) resulted in statistically significant and clinically meaningful improvement in survival among patients with metastatic **colorectal cancer**. The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($p < 0.001$). The median duration of progression-free survival was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo (hazard ratio for disease progression, 0.54; $p < 0.001$). The corresponding rates of response were 44.8% and 34.8% ($p = 0.004$).

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 (hazard ratio for death, 0.79; $p = 0.003$) with the risk of increased treatment-related deaths [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 (EMEA) 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 trail 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 Ixabepilone (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-azabicylo[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 dexverapamil. 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 ketaconazole), 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.

Toxicology [19].

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/m^2). 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; hypospermia; 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 hypospermia.

In conclusion, the STD10 was estimated to be 12.3 mg/kg (approximately 74 mg/m^2). 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/m^2, 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/m^2, a dose higher than the single dose of 74 mg/m^2 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/m^2) or paclitaxel at 48 mg/kg (144 mg/m^2), 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/m^2 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/m^2, 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/m^2/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/m^2/d was identified as the maximum tolerated dose (MTD) without GCSF, and is the recommended phase II dose. A dose $\geq$ 8 mg/m^2/d was administered in 48 cycles to 20 pts. All

patients received a dose ≥ 6 mg/m^2/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/m^2/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 $t_{1/2}\alpha$ of 115 ± .062 hours, a $t_{1/2}\beta$ of 12.7 ± 4.4 hours, a Vd_{ss} of 8.08 ± 3.99 L/kg, and a clearance of 419 ± 123 ml/min/m^2. 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/m^2/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 signaling pathways may have significant anti-tumor activity.

Based on these pre-clinical observations, several anti-angiogenic compounds have been successfully investigated. Sorafinib, 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 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.

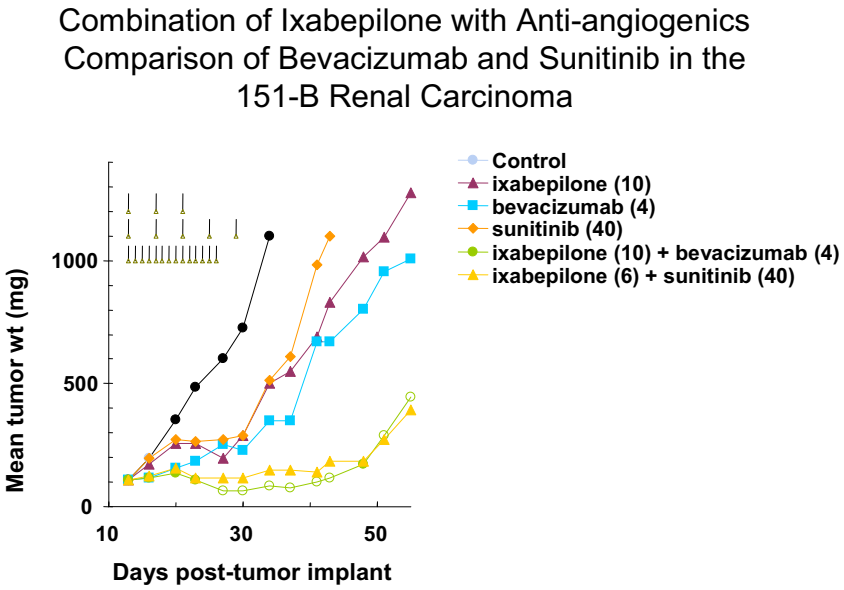
The FDA approved sorafenib (Nexavar®) and sunitinib (Sutent®) in December 2005 and February 2006 respectively based on objective responses and improvement in progression-free survival [49]. In May 2007, the FDA approved the mTOR inhibitor temsirolimus (Torisel®), based on improvement in survival in a 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:

$$\text{Tumor weight} = (\text{length} \times \text{width}\ 2) \div 2$$

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:



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 **3.4.6** and **Appendix A**).

1.2.6 Dose and Design Rationale

In this combination phase II study, the starting dose and dosing interval of ixabepilone (6 mg/m^2 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 ELIGIBILITY CRITERIA

Subjects meeting all of the following criteria will be considered for enrollment into the study

2.1.1 Pathologic confirmation of metastatic or unresectable renal cell carcinoma with predominant clear cell histology (>70%) by the Laboratory of Pathology, NCI or the Medical University of South Carolina.

2.1.2 Progression on or after stopping treatment with an agent approved by the FDA for the treatment of RCC. Patients must have received at least one FDA approved agent (axitinib, sunitinib, sorafenib, pazopanib, temsirolimus, IL-2, interferon or everolimus). Patients must be off prior IL-2 or interferon for 4 weeks prior to entry. They must be off sunitinib, sorafenib, pazopanib, axitinib, temsirolimus or everolimus or other TKIs for 2 weeks prior to entry.

2.1.3 Eighteen years of age or older.

2.1.4 ECOG performance status ≤ 2.

2.1.5 Resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE v.3.0 through 12/31/10 and version 4.0 beginning 1/1/11 grade ≤ 1 and to baseline laboratory values as defined in inclusion criterion **2.1.6**.

2.1.6 Adequate organ and bone marrow function as evidenced by:

2.1.6.1 hemoglobin ≥ 9.0 g/dL

2.1.6.2 absolute neutrophil count ≥ 1.5 x 10^9/L

2.1.6.3 platelet count ≥ 100 x 10^9/L

2.1.6.4 creatinine ≤ 1.5 x ULN, OR measured creatinine clearance ≥ 40 ml/min

2.1.6.5 urinalysis </= 1+ protein (equivalent of less than or equal to 30 mg/dL) or a 24 hour urine protein less than 500 mg. If the urinalysis is >1 +, obtain a random protein creatinine

ratio (UPC). If protein > 30 mg/dl then obtain a 24 hour collection to demonstrate total protein is less than 500 mg

2.1.6.6 AST/SGOT and ALT/SGPT ≤ 2.5 x ULN (or ≤ 5 x ULN if liver function abnormalities due to underlying malignancy)

2.1.6.7 Total bilirubin ≤ 1.5 x ULN

2.1.7 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.

2.1.8 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).

2.1.9 Subjects must agree to sign and date an Institutional Review Board (IRB)-approved subject informed consent form.

2.1.10 Subjects must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

2.1.11 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:

2.2.1 Invasive procedures defined as follows:

2.2.1.1 Major surgical procedure, open biopsy or significant traumatic injury within 6 weeks prior to Day 1 therapy

2.2.1.2 Anticipation of need for major surgical procedures during the course of the study

2.2.1.3 Minor surgery, such as port-a-cath placement, and dental procedures, within 2 weeks.

2.2.1.4 (There will be no delay for percutaneous core biopsies or PICC/IJ line placement)

2.2.2 Cumulative radiation therapy to > 25% of the total bone marrow.

2.2.3 History of uncontrolled or labile hypertension, defined as blood pressure > 160/90 mm Hg (NCI CTCAE v.3.0 through 12/31/10 and version 4.0 beginning 1/1/11 grade ≥ 2), on at least 2 repeated determinations on separate days within 15 days prior to study enrollment.

2.2.4 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.

2.2.5 Symptomatic spinal cord compression.

2.2.6 Evidence of clinically significant bleeding diathesis or underlying coagulopathy.

2.2.7 Antiretroviral therapy for HIV disease.

2.2.8 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.

2.2.9 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.

2.2.10 Prior therapy with bevacizumab

2.2.11 Prior therapy with ixabepilone.

2.2.12 Patients on anticoagulant therapy will be evaluated on a case by case basis for inclusion.

2.2.13 Serious or non-healing wound, ulcer or bone fracture

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

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

2.2.16 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.

2.2.17 Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies

2.2.18 Patients receiving CYP3A4 inhibitors in section **3.6** that cannot be discontinued.

2.3 BASELINE EVALUATION

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

2.3.1.1 Measurable disease, detailed sites of tumor

2.3.1.2 Narcotic use and pain assessment and

2.3.1.3 Prior therapies (surgical, radio therapeutic, and molecular-targeted therapies).

2.3.1.4 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.

2.3.2 Medically Indicated Imaging Studies (Baseline) –

2.3.2.1 CT scan of 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.

2.3.2.2 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.

2.3.2.3 An EKG should be obtained within 16 days of enrollment.

2.3.2.4 Laboratory Evaluation [baseline is to be obtained within 4 days prior to enrollment.

2.3.3 Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time.

2.3.4 Biochemical Profile: Serum electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, magnesium, amylase, lipase.

2.3.5 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.

2.3.6 Urinalysis.

2.3.7 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 the NCI Laboratory of Pathology or the Medical University of South Carolina.

2.4 REGISTRATION PROCEDURES

2.4.1 On-Study Procedure

Maureen Edgerly, RN (office 435-5604, pager 102-10728) must be notified prior to enrolling any patients on study.

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757.

After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents.

Verification of Registration will be forwarded electronically via e-mail. Please note it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

2.4.2 For Participating Site Registration

All patients must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. A protocol registration form and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To register a subject, fax the completed registration checklist and cover memo to the CRO at 301-480-0757. Please indicate on the protocol registration form whether the patient is screening or is eligible to start treatment. The CRO will notify you either by e-mail or fax that the protocol registration form has been received. The CRO will assign a unique patient/subject ID number for each subject that will be used to enter data into the C3D data base. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Maureen Edgerly, RN, 301-435-5604, edgerlym@mail.nih.gov. Technical questions about the form should be directed to the Central Registration Office (301-402-1732).

2.4.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 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 Biochemical Profile: Serum electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, and magnesium.
- Imaging studies: CT or MRI (obtained within 16 days prior to study entry).

3.1.2 Within 5 days of every restaging cycle (following the second, fourth and sixth cycles, and then every second or 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 Biochemical Profile: Serum electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, and magnesium.
- Imaging studies: CT or MRI of known/suspected areas of disease

3.1.3 Within 5 days of every cycle:

- History and physical examination (for medical record only; not for Research record).
- Laboratory studies: CBC with differential, platelet count, and Biochemical Profile: Serum electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, calcium, phosphorous, albumin, magnesium, and urinalysis.

3.1.4 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.

3.1.5 Safety analysis of the first 6 patients:

This has been completed and there were no clinically significant unexpected toxicities.

3.1.6 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. Bevacizumab will be administered on day 1 of each cycle whenever possible, however when circumstances prevent administering bevacizumab on day 1, ixabepilone will begin on day 1 and bevacizumab may be given on day 2. Such circumstances could include the collection of a 24 hr urine sample to determine proteinuria, clinical judgment, scheduling difficulties or drug supply. A cycle consists of 3 weeks or 21 days +/- 3 days. Following cycle 6, cycles will be spread out to 4 weeks or 28 days +/- 3 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.

3.1.7 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.

3.1.8 Reassessment

Patients will be seen in clinic at least every 3 weeks. A history and physical with sphygmomanometry 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 following the second, fourth and sixth cycles. After the sixth cycle, the CT scans will be obtained and reviewed every second or third cycle) to monitor disease response. Measurable disease will be monitored as described in section **5.2**. Treatment 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 sphygmomanometer 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 **3.3** 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 and a measurement of blood pressure should be performed. Dose timing adjustments are listed in section **3.3**.

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.

3.2.1.1 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 section **3.3**
- 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 mediation should be initiated or increased for optimal BP control according to standard public heath guidelines. Please refer to section **3.3** for dose modification information related to hypertension.
- Proteinuria: Proteinuria will be monitored by urinalysis every cycle.
- Surgery and wound complication issues: 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 should 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/m^2/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.

3.2.2.1 **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 H_1 antagonist (may consist of diphenhydramine 50 mg or equivalent H1 antagonist) and
b) Oral H_2 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)

Diphenhydramine dosing may be decreased to 25 mg or 12.5 mg daily if somnolence becomes problematic. Cycle one should be given at 50 mg daily and reductions can be made at subsequent cycles. Infusion reactions seldom occur, but have occurred most often during cycle one.

If a subject experiences a hypersensitivity reaction with oral H_1 and H_2 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:

a) 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.

b) Begin ixabepilone at 25% of the previous rate for 1 hour;
c) 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

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
Allergic reactions Or **Infusion-related reactions** Or **Anaphylaxis**	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • 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. • Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial), arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)	[Note: Patients with primary lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	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 full-dose

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
		anticoagulation **IF** all of the criteria below are met: - 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 - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg) – Grade 3 (SBP ≥160 mmHg or DBP ≥100 mmHg)	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg* • For hypertension that is refractory requiring delay of bevacizumab for > 4 weeks, discontinue bevacizumab
	Grade 4 (Hypertensive	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
	crisis or malignant hypertension)	
Heart Failure OR **Left Ventricular (LV) dysfunction**	• Heart failure ≥Grade 2 • LV dysfunction ≥Grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis dipstick. If Dipstick ≥2+ proteinuria, 24-hour urine protein should be obtained	Dipstick ≥ 2+	Hold bevacizumab and obtain 24 hour urine protein
	If 24-h urine protein <2g	Continue bevacizumab
	If 24-h urine protein ≥2 g	• Hold bevacizumab until 24-hour urine protein <2.0 g • Discontinue bevacizumab if urine protein does not recover to < 2.0 g after 8 weeks of bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• 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 hemoglobin 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
Hemorrhage (not CNS or pulmonary)	Grade 3	• 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 hemoglobin is stable - there is no bleeding diathesis that

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
		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.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome OR **PRES** (Posterior Reversible Encephalopathy Syndrome)	Any Grade	Discontinue bevacizumab upon diagnosis of RPLS.
Wound dehiscence OR **Wound complications**	Grade 2	Hold bevacizumab until healing
	Grade 3-4	Discontinue bevacizumab
Perforation (GI, or any other organ)	Any Grade	Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)	Any Grade	Discontinue bevacizumab
Obstruction of GI tract	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after 28 days and full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to≤Grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤Grade 1 and unlikely to recur with retreatment.

Note 1: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below

Note 2: If bevacizumab is interrupted for ANY reasons for >4 weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol.

3.3.1.1 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.

3.3.1.2 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 **3.3.2**).

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:

3.3.2.1 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/mm^3 and the platelet count is above 75,000/mm^3). 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 Reductions for Hematologic Toxicities

Toxicity	Dose Adjustment
ANC Count ≤ 500 cells/mm^3 for ≥ 4 days	Reduce ixabepilone to 4.5mg/m^2 level
Platelet count ≤ 50,000 cells/mm^3	Reduce ixabepilone to 4.5mg/m^2 level
Delay in starting cycle > 2 weeks	Reduce ixabepilone to 4.5mg/m^2 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.

Toxicity grade:	**ixabepilone dose:**
1	unchanged
2	unchanged
3[Note 1]	reduce ixabepilone dose to 4.5mg/m^2 level.
4[Note 2]	reduce ixabepilone dose to 4.5mg/m^2 level.

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 **3.10** 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.

These translational studies will be obtained only if subjects are participating at the NCI site in Bethesda. Subjects enrolled at other sites will not participate in these translational studies.

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

	Baseline	C1/D5	C2/D1	Every two cycles (cycle 4, day 1 etc.)
Tumor biopsy	X		X	
Blood samples	X	X	X	X
Imaging DCE-MRI	X	X		X

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

3.4.2.1 Protein profiling: Blood samples (16 ml in SST) will be collected before protocol treatment (T0), cycle 1 day 5, then at day 1 of cycles 2, 4 and 6, prior to study drug administration and immediately centrifuged. Serum will be stored at -80°C until assay. Quantitative determination of serum VEGF-A, soluble VEGFR2 and -3, βFGF, will be performed using the ELISA method. In addition erythropoietin level will be determined

at the same time as a putative indirect maker of activity. Samples will be processed in the laboratory of Tito Fojo.

3.4.2.2 Tumor Endothelial Markers (TEMs, [53]): Blood samples (8 ml in SST) tube will be collected before (T0), cycle 1 day 5, then at day 1 of cycles 2, 4 and 6 and immediately centrifuged. Serum will be stored at -80°C until assay. Samples will be processed in the laboratory of Tito Fojo and Dr. St. Croix will receive the serum aliquots labeled with study identifiers from Fojo's lab. Patients' names will not be included on the serum aliquot labels.

Dr. St. Croix's laboratory is in the process of developing an ELISA-based serum test in order to detect angiogenesis in cancer patients. Such an assay is urgently needed in order to determine the optimal biological dose of over 30 anti-angiogenic agents in clinical trials. The assay is based on antibodies developed in Dr. St. Croix's laboratory that recognize the native form of various soluble Tumor Endothelial Markers (TEMs) such as TEM7s, TEM8s, CD137s, CD276s and Apelin. The sandwich ELISA involves coating of a 96-well plate with a capture antibody, capture of the soluble TEM from serum or plasma, and then detection of the captured TEM using an enzyme-linked anti-TEM antibody that recognizes an alternative epitope present on the immobilized soluble TEM. The assay has been developed using recombinant soluble TEM proteins and anti-TEM antibodies. Dr. St. Croix now wishes to test the assay using serum from individuals with kidney cancer, before and following anti-angiogenic treatment. The baseline level of soluble TEMs in kidney cancer patients will also be compared with serum derived from normal disease free-individuals which is already available to Dr. St. Croix. If possible, individuals taking prescription medications (i.e. pharmaceuticals) or anti-inflammatory agents on a regular basis should be excluded. Also, those with known chronic diseases (e.g. autoimmune or inflammatory disease) should be excluded.

3.4.2.3 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.

3.4.3 Storage, Tracking, Protocol Completion and Sample Destruction:

3.4.3.1 CEL Tracking:

These samples will be delivered directly to **Jane Trepel's lab** for processing. They will be tracked in a computerized database in the Jane Trepel'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 Jane Trepel's 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. Fojo's lab for storage as outlined below.

3.4.3.2 Protein profiling and TEMs

These blood samples will be stored in the laboratory of Dr. Fojo and tracked in a computerized database in Dr. Fojo's laboratory. The freezers are located on site in or near Dr. Fojo's labs on the 12th and 13th floors of Bldg 10. 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. Fojo'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. If Dr. St. Croix or Jane Trepel have samples remaining once they have completed all studies associated with the protocol, they must return the samples to Dr. Fojo's lab.

3.4.4 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.

3.4.4.1 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 laboratory of Maria Merino, MD in the NIH/NCI Department of Surgical Pathology, Bldg 10, Rm 2B50 and tracked according to Surgical Pathology SOP.

3.4.4.2 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 Jane Trepel.

3.4.5 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 is 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. Fojo's laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

3.4.6 Imaging Studies

3.4.6.1 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_{trans} and k_{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.**

3.4.7 Blood Samples for Clinical and Research Purposes:

Volume of collection

	Baseline Eligibility	C1D1	C1D5	Weekly	C2	Every cycle	Cycle 4 & 6
Protein profiling (Fojo lab)		16	16		16		16
Circulating Endothelial Cells (Trepel lab)		24	24		24		
Tumor Endothelial Markers (St Croix lab)		8	8		8		8

	Baseline Eligibility	C1D1	C1D5	Weekly	C2	Every cycle	Cycle 4 & 6
TOTAL Research (ml)		**48**	**24**		**48**		**24**
Clinical labs (CBC, coags, Biochemical Profile)	15	12		6	12	12	12
Total Research and Clinical labs (ml)	**15**	**60**	**24**	**6**	**60**	**12**	**36**

3.5 STUDY CALENDAR

Study Procedure	Screen	Study Treatment [a]							Follow-Up [b]			
		Cycle 1 (Days 1 - 21)						Cycle 2 Day 1	Each Cycle	Every 2-3 cycles	Off Treat-ment	Every 3 months off treatment
		D1	D2	D3	D4	D5						
Baseline Documentation												
Informed Consent and Contraceptive Counseling	X											
Medical/Oncological History and Demographics	X											
Baseline Signs and Symptoms		X										
Physical Examination	X	X						X#	X#		X#	
Laboratory Studies												
Hematology [1]	X	X						X#	X#		X#	
Blood Chemistry	X	X						X#	X#		X#	
Coagulation	X								X#		X#	
Pregnancy Test	X								X#		X#	
Urinalysis	X	X						X#	X#		X#	
Electrocardiogram	X											
Study Treatment*												
BEVACIZUMAB (15 mg/kg)		X							X			
IXABEPILONE		X	X	X	X	X			X			
Tumor Assessments												
Tumor Imaging (Standard)	X									X#	X#	X#
DCE-MRI	X*	X								X#		
Other Clinical Assessments												
Adverse Events		X						X	X		X	
Concomitant Medications and Treatments		X						X	X		X	

Study Procedure	Screen	Study Treatment [a]							Follow-Up [b]			
		Cycle 1 (Days 1 - 21)						Cycle 2 Day 1	Each Cycle	Every 2-3 cycles	Off Treat-ment	Every 3 months off treatment
		D1	D2	D3	D4	D5						
Research samples												
Tumor biopsy		X						X				
Research blood samples		X				X		X				

*: within 7 days prior Day1. [1]:CBC with platelet count will be monitored weekly
#: within 5 days of restaging

3.6 CONCURRENT THERAPIES

3.6.1 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: delaviridine, nelfinavir, ampenavir, ritonavir, indinair, 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,

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

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 non-compliance or 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 POST TREATMENT 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. Scans will be reviewed at the NCI or the Medical University of South Carolina to document time to progression.
3. 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 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 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 C3D standard database used for study data at the NCI. Complete records must be maintained on each patient participating in this trial and retained for at least two years following the notification date of closure. The study will be monitored by NCI CTEP per their standard procedures for Phase II studies (see section **8.4** for more details).

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).

Special Note: Record only the highest grade of the adverse events hypertension or hypotension (and the dates corresponding to the highest grade) during a seven day (Days 1-7, 8-14, 15-21, etc.).

The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored in locked cabinets and in a password protected database until it is no longer of scientific value.

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

Data will not be distributed outside NIH without IRB notification.

Dr. Fojo will continue to have access to the data for purposes of data analysis and publication when he is at Columbia University. He will have access to the data via a secure flash drive. It is also possible that data will be sent to him via encrypted email.

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 international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

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 with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

5.2.2 Guidelines 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.

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

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 when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). 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. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require

sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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

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

5.2.3 Evaluation of Response

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [30]. Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and 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 Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

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

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 (see section **5.2.3**).

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

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

5.2.4 Confirmatory Measurement/Duration of Response Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol see section **5.2.4**

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).

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. Disease must show an absence of progression for a period of at least 6 weeks as verified by serial CT scans to be classified as stable disease.

Reporting of Results

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

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

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

5.3 TOXICITY CRITERIA

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

6 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.

7 HUMAN SUBJECT PROTECTIONS

7.1 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. All individuals with RCC (clear cell) that is refractory to VEGFR inhibitors are eligible according to the eligibility criteria within section 2. 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 2. 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.

7.2 PARTICIPATION OF CHILDREN

Patients under the age of 18 will be excluded from study.

7.3 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.

7.4 RISKS/BENEFITS ANALYSIS

7.4.1 Potential Risks

7.4.1.1 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 NIH's Clinical Center in Bethesda, Maryland. 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.

7.4.1.2 Risk of Treatment:

Details of the risk of drug therapy are detailed in section 8.5.

7.4.1.3 Risks of radiation exposure:

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

7.5 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.

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 DEFINITIONS

8.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **5.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse

events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **8.2**, **8.3**, and **8.4**.

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

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

8.1.2 Suspected adverse reaction

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

8.1.3 Unexpected adverse reaction

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

8.1.4 Serious

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

8.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization

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

8.1.6 Disability

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

8.1.7 Life-threatening adverse drug experience

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

8.1.8 Protocol Deviation (NIH Definition)

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

8.1.9 Non-compliance (NIH Definition)

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

8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

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

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

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

8.2 NCI-IRB REPORTING

8.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease

- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

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

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

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

8.2.3 NCI-IRB Reporting of IND Safety Reports

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

8.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

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

8.4 CTEP REPORTING REQUIREMENTS

8.4.1 Expedited Data Reporting

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3	Grade 3	Grades 4 & 5[2]	Grades 4 & 5[2]

	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected	Expected
				with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization		
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
Grade 4 and Grade 5 unexpected events
CTEP-AERS 10 calendar day report:
Grade 3 unexpected events with hospitalization or prolongation of hospitalization
Grade 5 expected events
[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.
December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Expedited AE reporting timelines defined:

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Expedited adverse event (AE) reporting for this study is via CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the secure CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents" which can be downloaded from the *CTEP web site* (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section **8.5** (Pharmaceutical Information).

8.4.2 Expedited Adverse Event Reporting Exclusions

Grade 3 or 4 myelosuppression, whether or not hospitalized, will not require expedited reporting via CTEP-AERS.

8.4.3 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS)

8.4.4 Routine Data Reporting

Adverse events will be reported to CTEP via a transfer from C3D database to CDUS (web-based application) on a quarterly basis, in addition to the expedited reporting described above.

8.5 DATA AND SAFETY MONITORING PLAN

8.5.1 Principal Investigator/Research Team

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

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

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

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)

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

1. Agents may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:
   Email: ncicteppubs@mail.nih.gov

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

9.2 MULTI-INSTITUTIONAL GUIDELINES

9.2.1 IRB Approvals

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

9.2.2 Amendments and Consents

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

9.2.3 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix D, Section **12.4**.

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

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

10 PHARMACEUTICAL INFORMATION

10.1 BEVACIZUMAB (NSC 704865)

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^{o} to 8^{o} 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.

10.1.1 Reported Adverse Events and Potential Risks: Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome[2]	
	Cardiac disorders - Other (supraventricular arrhythmias)[3]		***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)***
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[2]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			

	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications – Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Cardiac troponin I increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[12]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular[2]	
	Peripheral sensory neuropathy[13]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	

	Hematuria		***Hematuria (Gr 3)***
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[14]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
		Vascular disorders - Other (arterial thromboembolic event)[2,15]	

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

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

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

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

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

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

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

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

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

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

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

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

Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis

CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction

EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes

GASTROINTESTINAL DISORDERS - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis;Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS

HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal

and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome

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

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

10.1.2 Major Adverse Events Associated with Bevacizumab Therapy.

A list of Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.3, August 1, 2013 terms is included in Section (**10.1.1**) of the protocol. Reference may also be made to the Investigators' Brochure and 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 protenuria 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).

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.

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/m^2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m^2, one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m^2); 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

10.1.3 Agent Ordering and Agent Accountability

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

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

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

10.2 IXABEPILONE (NSC 710248)

Chemical Name: (1S,3S,7S,10R,11S,12S,16R)-7,11-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: BMS-247550, Epothilone B analog, Ixempra®

Classification: Epothilone B analog

Molecular Formula: $C_{27}H_{42}N_2O_5S$ **M.W.:** 506.7 grams/mole

Mode of Action: Ixabepilone is a semi-synthetic analog of the natural product epothilone B. The epothilones are a novel class of non-taxane microtubule-stablizing

agents obtained from the fermentation of cellulose degrading myxobacteria, *Sorangium cellulosum.*

How Supplied: Ixabepilone is supplied as a kit containing one vial of ixabepilone and one vial of diluent. Ixabepilone appears as a lyophilized, white to off-white color, whole or fragmented cake in a vial. The drug product is available in 15 mg vials.

The diluent is a mixture of 52.8% polyoxyethylated castor oil and 39.8% dehydrated alcohol, USP. Each vial contains 8 mL.

Reconstitute the drug vial with the provided diluent only.

Preparation: Prior to constitution of the ixabepilone, the kit should be removed from the refrigerator and allowed to stand at room temperature for approximately 30 minutes. When first removed from the refrigerator, a white precipitate may appear in the diluent vial. The precipitate will disappear once the diluent reaches room temperature.

Slowly inject 8 mL of the diluent into the 15 mg vial. Gently swirl and invert the vial until the ixabepilone powder is dissolved completely. This results in a 2mg/mL solution.

Further dilute the ixabepilone solution to a final concentration of 0.2 mg/mL to 0.6 mg/mL in a non-PVC container before administration to the patient with one of the following infusion solutions:

- Lactated Ringer's Injection, USP
- 0.9% Sodium chloride Injection, USP
  When using a 250 mL or a 500 mL bag of 0.9% Sodium Chloride Injection to prepare the infusion, the pH must be adjusted to a pH between 6.0 and 9.0 by adding 2 mEq of Sodium Bicarbonate Injection, **prior** to the addition of the constituted Ixabepilone solution.
- PLASMA-LYTE A Injection pH 7.4®

Storage: Store ixabepilone kits in the refrigerator (2° to 8°C) prior to use and keep the kit contents intact to protect from light.

Stability: 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.** Administration of diluted ixabepilone must be completed within this 6 hour period.

Route of Administration: Administer the ixabepilone infusion intravenously through an appropriate in line filter with a microporous membrane of 0.2 to 1.2 microns. Any remaining solution should be discarded according to institutional procedures for antineoplastics.

Incompatibilities: DEHP-free infusion containers and administration sets must be used.

IV sets and components typically used for the administration of paclitaxel are compatible with ixabepilone infusions.

Potential Drug Interactions: Ixabepilone is a CYP3A4 substrate.

Patients with a history of a severe hypersensitivity reaction to agents containing Cremophor® EL or its derivatives (e.g., polyoxyethylated castor oil) should not be treated with Ixabepilone.

All patients should be premedicated with an H1 and an H2 antagonist approximately 1 hour before Ixabepilone infusion and be observed for hypersensitivity reactions (e.g., flushing, rash, dyspnea, and bronchospasm). In case of severe hypersensitivity reactions, the Ixabepilone infusion should be stopped and aggressive supportive treatment (e.g., epinephrine, corticosteroids) started. Patients who experience a hypersensitivity reaction in one cycle of Ixabepilone must be premedicated in subsequent cycles with a corticosteroid in addition to the H1 and H2 antagonists, and extension of the infusion time should be considered..

10.2.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ixabepilone (BMS 247550, NSC 710428)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1572 patients.* Below is the CAEPR for ixabepilone (BMS 247550, ixempra).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, February 28, 2013[1]

Adverse Events with Possible Relationship to Ixabepilone (BMS 247550, ixempra) (CTCAE 4.0 Term) [n= 1572]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Adverse Events with Possible Relationship to Ixabepilone (BMS 247550, ixempra) (CTCAE 4.0 Term) [n= 1572]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
	Atrial fibrillation		***Atrial fibrillation (Gr 2)***
	Atrial flutter		***Atrial flutter (Gr 2)***
	Paroxymal atrial tachycardia		***Paroxymal atrial tachycardia (Gr 2)***
	Sinus bradycardia		***Sinus bradycardia (Gr 2)***
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr 2)***
EYE DISORDERS			
	Watering eyes		***Watering eyes (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
		Ileus	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Radiation recall reaction (dermatologic)		***Radiation recall reaction (dermatologic) (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
Alkaline phosphatase increased			***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Creatinine increased		
	INR increased		***INR increased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***

Adverse Events with Possible Relationship to Ixabepilone (BMS 247550, ixempra) (CTCAE 4.0 Term) [n= 1572]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Platelet count decreased			***Platelet count decreased (Gr 4)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		***Tumor pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Dysphasia		***Dysphasia (Gr 2)***
	Headache		
	Neuralgia		***Neuralgia (Gr 2)***
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 3)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 3)***
	Syncope		***Syncope (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
	Urinary retention		***Urinary retention (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Hiccups		***Hiccups (Gr 2)***
	Hypoxia		***Hypoxia (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
		Pleural effusion	
	Pneumonitis		***Pneumonitis (Gr 3)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
		Erythema multiforme	
	Nail loss		***Nail loss (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

Adverse Events with Possible Relationship to Ixabepilone (BMS 247550, ixempra) (CTCAE 4.0 Term) [n= 1572]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
VASCULAR DISORDERS			
		Capillary leak syndrome	***Capillary leak syndrome (Gr 2)***
	Flushing		***Flushing (Gr 2)***
	Hypotension		***Hypotension (Gr 2)***

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

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

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

Also reported on ixabepilone (BMS 247550, ixempra) trials but with the relationship to ixabepilone (BMS 247550, ixempra) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation

CARDIAC DISORDERS - Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion

EYE DISORDERS - Blurred vision; Conjunctivitis

GASTROINTESTINAL DISORDERS - Colitis; Dry mouth; Dyspepsia; Dysphagia; Esophagitis; Gastrointestinal disorders - Other (impaired gastric emptying); Gastrointestinal perforation[3]; Rectal hemorrhage; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Edema trunk; Injection site reaction; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Infections and infestations – Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cardiac troponin T increased; Lymphocyte count decreased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypernatremia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain

NERVOUS SYSTEM DISORDERS - Ataxia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Seizure; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal hemorrhage; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Epistaxis; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Skin and subcutaneous tissue disorders - Other (pigmentation changes); Urticaria

VASCULAR DISORDERS - Hot flashes; Hypertension; Phlebitis; Thromboembolic event

Note: Ixabepilone (BMS 247550, ixempra) 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.

10.2.2 Agent Ordering and Agent Accountability

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

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

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

10.3 DIPHENHYDRAMINE HYDROCHLORIDE (HCL) INJECTION

10.3.1 General Issues:

Diphenhydramine hydrochloride (Benadryl) is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N, N-dimethylethylamine 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 $C_{17}H_{21}NO \cdot HCl$.

10.3.2 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.

10.4 RANITIDINE HYDROCHLORIDE (HCL) INJECTION:

10.4.1 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-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride. The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

10.4.2 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^{o}C and 30^{o}C and protected from light and excessive heat. The premixed infusion solution should be stored between 2^{o}C and 25^{o}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.

11 REFERENCES

1. Christian, B., 26-Week intravenous toxicity study with rhuMAb VEGF in cynomolgus monkeys with a 12 week recovery. 1999, Genetech Report: South San Francisco. p. 97-194.
2. Ryan, A.M., et al., Preclinical safety evaluation of rhuMAbVEGF, an antiangiogenic humanized monoclonal antibody. Toxicol Pathol, 1999. 27(1): p. 78-86.
3. Ferrara, N., et al., Vascular endothelial growth factor is essential for corpus luteum angiogenesis. Nat Med, 1998. 4(3): p. 336-40.
4. Gordon, M.S., et al., Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol, 2001. 19(3): p. 843-50.
5. Margolin, K., et al., Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. J Clin Oncol, 2001. 19(3): p. 851-6.
6. Yang, J.C., et al., A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med, 2003. 349(5): p. 427-34.
7. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jun 3;350(23):2335-42.
8. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50. Erratum in: N Engl J Med. 2007 Jan 18;356(3):318.
9. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005 Feb 1;23(4):792-9.
10. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007 Dec 27;357(26):2666-76.
11. Lin A, Rugo HS. The role of trastuzumab in early stage breast cancer: current data and treatment recommendations. Curr Treat Options Oncol. 2007 Feb;8(1):47-60.
12. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, Chevreau C, Filipek M, Melichar B, Bajetta E, Gorbunova V, Bay JO, Bodrogi I, Jagiello-Gruszfeld A, Moore N; AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007 Dec 22;370(9605):2103-11.
13. Yang, R., et al., Effects of vascular endothelial growth factor on hemodynamics and cardiac performance. J Cardiovasc Pharmacol, 1996. 27(6): p. 838-44.
14. Shen, B.Q., D.Y. Lee, and T.F. Zioncheck, *Vascular endothelial growth factor governs endothelial nitric-oxide synthase expression via a KDR/Flk-1 receptor and a protein kinase C signaling pathway.* J Biol Chem, 1999. 274(46): p. 33057-63.

15. Ostendorf, T., et al., *VEGF(165) mediates glomerular endothelial repair.* J Clin Invest, 1999. 104(7): p. 913-23.
16. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, Chevreau C, Filipek M, Melichar B, Bajetta E, Gorbunova V, Bay JO, Bodrogi I, Jagiello-Gruszfeld A, Moore N; AVOREN Trial Investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007 Dec 22;370(9605):2103-11.
17. Donovan D, Vahdat LT. Epothilones: clinical update and future directions. Oncology (Williston Park). 2008 Apr 15;22(4):408-16
18. Structure-Activity Relationships of the Epothilones and the First In Vivo Compariosn with Paclitaxel. Su, D-S., Balog, A., Men, D., Bertinato, P., Danishefsky, S.J., Zheng, Y-H., Chou, T-C., He, L.., and Horwitz, S.B. Angew Chem. Int. Ed. Engl. 36: 2093-2096 (1997).
19. Investigator Brochure: BMS-247550. Epothilone Analog. Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, P.O. Box 5100, Wallingford Connecticut 06492-7660.
20. Epothilones, a New. Class of Microtubule-stabilizing Agents with a Taxol-like Mechanism of Action. Bollag, D.M., Mc Queney, P.A., Zhu, J., Hensens, O., Koupal, L., Liesch, J., Goetz, M., Lazarides, E., and Woods, C.M. Cancer Res. 55: 2325-2333 (1995).
21. Abraham J, Agrawal M, Bakke S, Rutt A, Edgerly M, Balis FM, Widemann B, Davis L, Damle B, Sonnichsen D, Lebwohl D, Bates S, Kotz H, Fojo T. Phase I trial and pharmacokinetic study of BMS-247550, an epothilone B analog, administered intravenously on a daily schedule for five days. J Clin Oncol. 2003 May 1;21(9):1866-73.
22. Anaphylactoid Reactions in Children Receiving High-dose Intravenous Cyclosporine for Reversal of Tumor Resistance: The Causative Role of Improper Dissolution of Cremophor EL. Theis J.G., Liau-Chu, M., Chan, H.S., Doyle, J., Greenberg, M.L., and Koren, G. J. Clin. Oncol 10:2508-16 (1995).
23. Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, Jassem J, Pivot XB, Klimovsky JV, de Mendoza FH, Xu B, Campone M, Lerzo GL, Peck RA, Mukhopadhyay P, Vahdat LT, Roché HH. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007 Nov 20;25(33):5210-7.
24. Vansteenkiste J, Lara PN Jr, Le Chevalier T, Breton JL, Bonomi P, Sandler AB, Socinski MA, Delbaldo C, McHenry B, Lebwohl D, Peck R, Edelman MJ. Phase II clinical trial of the epothilone B analog, ixabepilone, in patients with non small-cell lung cancer whose tumors have failed first-line platinum-based chemotherapy. J Clin Oncol. 2007 Aug 10;25(23):3448-55.
25. Zhuang SH, Hung YE, Hung L, Robey RW, Sackett DL, Linehan WM, Bates SE, Fojo T, Poruchynsky MS. Evidence for microtubule target engagement in tumors of patients receiving ixabepilone. Clin Cancer Res. 2007 Dec 15;13(24):7480-6.
26. Whitehead RP, McCoy S, Rivkin SE, Gross HM, Conrad ME, Doolittle GC, Wolff RA, Goodwin JW, Dakhil SR, Abbruzzese JL. A Phase II trial of epothilone B analogue BMS-247550 (NSC #710428) ixabepilone, in patients with advanced pancreas cancer: a Southwest Oncology Group study. Invest New Drugs. 2006 Nov;24(6):515-20.
27. Galsky MD, Small EJ, Oh WK, Chen I, Smith DC, Colevas AD, Martone L, Curley T, Delacruz A, Scher HI, Kelly WK. Multi-institutional randomized phase II trial of the epothilone B analog ixabepilone (BMS-247550) with or without estramustine phosphate in

patients with progressive castrate metastatic prostate cancer. J Clin Oncol. 2005 Mar 1;23(7):1439-46.
28. Aghajanian C, Burris HA 3rd, Jones S, Spriggs DR, Cohen MB, Peck R, Sabbatini P, Hensley ML, Greco FA, Dupont J, O'Connor OA. Phase I study of the novel epothilone analog ixabepilone (BMS-247550) in patients with advanced solid tumors and lymphomas. J Clin Oncol. 2007 Mar 20;25(9):1082-8.
29. Denduluri N, Swain SM. Ixabepilone for the treatment of solid tumors: a review of clinical data. Expert Opin Investig Drugs. 2008 Mar;17(3):423-35.
30. Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS. Epidemiology of renal cell carcinoma In: Vogelzang NJ, ed. Comprehensive Textbook of Genitourinary Oncology. Philadelphia: Lippincott Williams & Wilkins, 1998.
31. Linehan WM, Klausner RD. Renal carcinoma. In: Vogelstein B, Kinzler K, eds. The genetic Basis of Human Cancer. New York: McGraw-Hill, 455 (1998).
32. Linehan WM, Bates SE, Yang JC. Cancer of the kidney In: Principles and Practices of Oncology. DeVita, VT, Hellman S. and Rosenberg SA. (Eds.). 7th Edition, J.B. Lippincott, Philadelphia, PA, 2004.
33. Schrader AJ, Olbert PJ, Hegele A, Varga Z, Hofmann R. Metastatic non-clear cell renal cell carcinoma: current therapeutic options. BJU Int. 2008 Jan 30
34. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.N Engl J Med. 2001 Dec 6;345(23):1655-9.
35. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001 Sep 22;358(9286):966-70.
36. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. J Urol 163(2):408 (2000).
37. Rosenberg SA, Lotze MT, Muul LM, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and Interleukin-2 or high-dose Interleukin-2 alone. NEJM 316(15):889-897, 1987.
38. Yang JC, Topalian SL, Parkinson D, et al: Randomized comparison of high-dose and low-dose intravenous interleukin-2 for the ttherapy of metastatic renal cell carcinoma: an interim report. J Clin Oncol 12(8): 1572-1576, 1994.
39. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma [see comments]. N Engl J Med 335:865 (1996).
40. Yagoda A, Abi-Bached B, Petrylak D. Chemotherapy for advanced renal cell carcinoma: 1983-1993. Semin Oncol 22:42 (1995).
41. Walther MM, Jennings SB, Gnarra JR, Zbar B, Linehan WM. Molecular genetics of renal cell carcinoma. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. Comprehensive Textbook of Genitourinary Oncology. Baltimore: Williams & Wilkins,160 (1996).
42. Zambrano NR, Lubensky IA, Merino MJ, Linehan WM, Walther MM. Histopathology and molecular genetics of renal tumors: toward unification of a classification system. J Urol 162:1246 (1999).
43. Ratain MJ, Eisen T, Stadler WM, et al: Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 24:2505-2512, 2006.

44. Escudier B, Szczylik C, Eisen T, et al: Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). J Clin Oncol 23:1093s, 2005.
45. Eisen T, Bukoswki RM, Staehler M, et al: Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC0: impact of crossover on survival). J Clin Oncol 24:223s, 2006 (suppl; abstr 4524).
46. Izzedine H, Billemont B, Thibault F, Rixe O. New challenges in kidney cancer therapy: sunitinib. Ann Oncol. 2007 Jul;18 Suppl 9:ix83-6.
47. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516-2524.
48. Motzer RJ, Hutson TE,Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. NEJM 2007; 356: 115-124.
49. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.N Engl J Med. 2001 Dec 6;345(23):1655-9.
50. Unnithan J, Rini BI. The role of targeted therapy in metastatic renal cell carcinoma. ScientificWorldJournal. 2007 Mar 2;7:800-7.
51. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.
52. Jain RK. Molecular regulation of vessel maturation. Nat Med. 2003 Jun;9(6):685-93.
53. Dillman RO: Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer Metastasis Rev 18:465-471, 1999
54. St Croix B, Rago C, Velculescu V, Traverso G, Romans KE, Montgomery E, Lal A, Riggins GJ, Lengauer C, Vogelstein B, Kinzler KW. Genes expressed in human tumor endothelium. Science. 2000 Aug 18;289(5482):1197-202.
55. Weidner N. Current pathologic methods for measuring intratumoral microvessel density within breast carcinoma and other solid tumors. Breast Cancer Res Treat. 1995;36(2):169-80.
56. Shojaei F, Wu X, Malik AK, Zhong C, Baldwin ME, Schanz S, Fuh G, Gerber HP, Ferrara N. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+Gr1+ myeloid cells. Nat Biotechnol. 2007 Aug;25(8):911-20.

12 APPENDICES

12.1 APPENDIX A: CYP3A4 MODULATORS

List of drugs that may have potential CYP3A4 interactions

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

CYP3A4 Inhibitors

Acetominophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

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

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

(1) Investigator's Brochure: Dasatinib (BMS 354825). Bristol-Myers Squibb. October 2006.

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

(3) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249.

Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329.

Updated on May 1, 2007

12.2 Appendix B: Daily Blood Pressure Log

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

Date	Time	Systolic	Diastolic	Heart Rate	*Additional Readings
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________
		1			↑no additional readings required
		2			4^{th} reading ______/________
		3			5^{th} reading ______/________

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

Date	Time	Systolic	Diastolic	Heart Rate	*Additional Readings
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________
		1			↑no additional readings required
		2			4th reading ______/________
		3			5th reading ______/________

12.3 APPENDIX C: NIH PROBLEM REPORT FORM

DDIR Approved v.1 6-11-2013 508-compliant

NIH PROBLEM REPORT FORM

Use this form to report problems to the IRB that may be:

A. Unanticipated Problems (UPs) including Unanticipated Adverse Device Effects (UADEs)
B. Protocol Deviations (PDs) or
C. Non-compliance

For more information on UPs and PDs, see SOP 16, "Principal Investigator (PI) and IRB Reporting Requirements for Unanticipated Problems and Protocol Deviations". For more information on Non-compliance, see SOP 16A, "Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP)."

DEFINITIONS

Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol.

The impact of a PD is characterized by designation as serious or not serious (see SOP 16- Appendix E.) PDs include three types of protocol deviations:

A. Those that occur because a member of the research team deviates from the protocol;
B. Those that are identified before they occur, but cannot be prevented (e.g., when a subject alerts the research team that inclement weather will prevent the subject from attending a scheduled protocol visit); and
C. Those that are discovered after they occur.

Unanticipated Problem (UP): Is any incident, experience, or outcome that meets **all** of the following criteria:

A. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

DHHS/NIH/OD/OIR/OHSRP 1

B. **Related or possibly related** to participation in the research (**possibly related** means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

C. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects; (See SOP 16A, "Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP).")

Minor non-compliance: Non-compliance that, is neither serious nor continuing.

Serious: A UP or PD is serious if it meets the definition of a Serious Adverse Event* or if it compromises the safety, welfare or rights of subjects or others.

* **Serious Adverse Event (SAE):** is any Adverse Event that: 1. Results in death; 2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3. Results in inpatient hospitalization or prolongation of existing hospitalization; 4. Results in a persistent or significant disability/incapacity; 5. Results in a congenital anomaly/birth defect; or 6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

NIH Problem Report Form v.1 6-11-2013

INSTRUCTIONS TO PRINCIPAL INVESTIGATORS

A. Use this form to report all problems to the IRB including UPs, PDs, or Non-compliance

B. Use the appropriate electronic IRB system to complete this form (iRIS or PTMS.) If the PI is unable to access the appropriate IRB reporting system, PI may use this NIH Problem Report Form. The PI may elect also to report events (especially if Serious) to the IRB Chair/designee and/or the CD, in person or by phone or e-mail. However, such reporting is in addition to the required reporting using the NIH Problem Report Form.

C. Any modifications to the protocol and/or consent(s) resulting from a UP, PD or Non-compliance must be submitted via a separate amendment in the appropriate IRB system (iRIS or PTMS), except when necessary to eliminate apparent immediate hazard to the subjects as explained in SOP 10 – "Amendments to IRB-approved Research".

D. Additional reporting requirements may apply, e.g., to the FDA, the NIH Office of Biotechnology Activities (OBA).

IMPORTANT: Notify the IRB and Clinical Director using the following timeframes:

A. **Serious UPs, UADEs, Serious PDs, and Serious Non-compliance:** as soon as possible, but not more than seven (7) days after the PI first learns of the event.

B. **Not Serious UP, Not Serious PD or Minor Non-compliance:** not more than fourteen (14) days after the PI first learns of the event.

NIH Problem Report Form v.1 6-11-2013

NIH PROBLEM REPORT FORM

Protocol #:	**Protocol Title:**
System Ref#: (*Enter the IRB System reference number for this submission*)	**Report version:** *(select one)* ☐Initial Report ☐Revised Report ☐Follow-up **If revised report or follow-up, enter the original System Ref #:**
Principal Investigator:	**Institute:** **Office Phone:** **E-mail:**
FDA Regulated Research *(indicate if this research is FDA regulated)* ☐YES ☐NO	Study Sponsor: IND/IDE# IND/IDE Name:
Date of problem:	**Location of problem:** *(e.g., NIH Clinical Center or Name of Site/Location)* ☐NIH CC ☐Other, specify:
Who identified the problem? *(provide role: nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable) (Do NOT include personal identifiers)*	Sex: ☐Male ☐Female Age: ☐Not applicable (more than subject is involved)
Diagnosis under study:	
If the subject is enrolled on any other studies, list the protocol number(s) here: *(If applicable, submit a separate report form for each protocol listed)*	
Is this problem? (*select all that apply*) ☐ An Unanticipated Problem that is: ☐Serious ☐ Not Serious ☐ A Protocol Deviation that is: ☐Serious ☐ Not Serious ☐ Non-compliance that is: ☐ Serious ☐Continuing	
Is the problem also *(select all that apply)* ☐AE ☐Non-AE	

DHHS/NIH/OD/OIR/OHSRP 4

NIH Problem Report Form v.1 6-11-2013

Name the problem: *(select all that apply)*
☐Adverse drug reaction
☐Abnormal lab value
☐Death
☐Cardiac Arrest/ code
☐Anaphylaxis
☐Sepsis/Infection
☐Blood product reaction
☐Unanticipated surgery/procedure
☐Change in status (e.g. increased level of care required)
☐Allergy (non-medication)
☐Fall
☐Injury/Accident (not fall)
☐Specimen collection issue
☐Informed consent issue
☐Ineligible for enrollment
☐Breach of PII
☐Tests/procedures not performed on schedule
☐Other, brief 1-2 word description:

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

Is this problem unexpected? *(i.e., event not described in protocol, consent, or Investigator Brochure)* ☐YES ☐NO **Please explain:**

Is this problem related or possibly related to participation in the research? ☐ YES ☐NO
Please explain:

Does the problem suggest the research places subjects or others at a greater risk of harm? ☐YES ☐ NO **Please explain:**

Have similar problems occurred on this protocol? ☐ YES ☐ NO
If "Yes", how many? Please describe:

NIH Problem Report Form v.1 6-11-2013

Describe what steps have you already taken as a result of this problem? **What steps do you plan to take as a result of the problem?** (*select all that apply*) ☐ No action required ☐ Amend consent (***Separate amendment submission required***) ☐ Amend protocol (***Separate amendment submission required***) ☐ Inform existing subjects (***Include example of information to be provided to subjects***) ☐ Close the protocol (***Separate closure submission required***) ☐ Temporarily halt the protocol (***Provide plan for management of enrolled subjects***) ☐ Increase frequency/type of safety or other monitoring **(Separate amendment submission required)** ☐ Other corrective action, describe:
In addition to the IRB, this problem is also being reported to: (*select all that apply*) ☐ IC Clinical Director ☐ Study Sponsor ☐ If Investigator-held IND/IDE, report to FDA ☐ Manufacturer: ☐ Institutional Biosafety Committee ☐ Office of Biotechnology Activities ☐ Data Safety Monitoring Board ☐ CC Occurrence Reporting System (ORS) ☐ Other: ☐ None of the above applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**
MEDICAL ADVISORY INVESTIGATOR'S SIGNATURE: *(if applicable)*	**DATE:**
CLINICAL DIRECTOR: *(If a UP, UADE, or a Serious PD)*	**DATE :**

12.4 APPENDIX D: CTEP MULTI-CENTER GUIDELINES

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

12.4.1 Responsibility of the Protocol Chair

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

12.4.2 Responsibilities of the Coordinating Center

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

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

12.4.3 Inclusion of Multicenter Guidelines in the Protocol

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

12.4.4 Agent Ordering

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

INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0057 PRINCIPAL INVESTIGATOR: Ravi Madan, M.D.

STUDY TITLE: A Phase II Multi-Center Study of Bevacizumab in Combination with Ixabepilone in Subjects with Advanced Renal Cell Carcinoma

Continuing Review Approved by the IRB on 06/22/15
Amendment Approved by the IRB on 08/13/15 (N) Date posted to web: 08/19/15
Standard

INTRODUCTION

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

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

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

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

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

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

Description of Research Study

This is a Phase II study for the experimental treatment of kidney cancer. A phase II study is one that begins the process of examining whether an experimental drug, or combination of drugs, might be useful in a particular type of cancer. The drugs to be examined in this study are a combination of ixabepilone and bevacizumab. The purpose of this phase II study is to determine whether the combination of ixabepilone administered for five consecutive days and bevacizumab administered on one day, both repeated every three weeks, is effective in the treatment of kidney cancer. 58 patients will be enrolled in this study.

Ixabepilone is a member of the epothilone class of chemotherapy drugs. The epothilones are drugs that interfere with the ability of cancer cells to divide. In the way they kill cells, they are very similar to a class of compounds known as the taxanes. The taxane class of drugs includes the drug taxol. Taxol has been used extensively in a wide variety of cancers and is effective in the treatment of several forms of cancer, including cancer of the breast, cancer of the ovary and cancer of the lung. The epothilones are similar to taxol, but also have other characteristics that may make them better. The latter include the ability to work in cells that are resistant to taxol. As of July 2008 we have enrolled 91 patients with advanced kidney cancer in a protocol where Ixabepilone was used as a single agent. Some have had shrinkage in their tumors and in some this has been followed by subsequent regrowth. Others have had progression of their disease and required discontinuation of their therapy. Others had neither shrinkage nor growth in their tumors for a period of several months. For a few this stable period lasted over a year, before the tumors began to grow again.

Ixabepilone is approved by the Food and Drug Administration (FDA) for the treatment of breast cancer that has spread beyond the breast to other parts of the body. The FDA approved the use of ixabepilone combined with another chemotherapy drug, capcitabine, and also to be used alone to treat breast cancer. It is also being studied to see if it might be effective in other types of cancer. We hope that ixabepilone will be useful as part of a combination therapy (several drugs used together) for the treatment of kidney cancer, as well as other cancers.

Bevacizumab is the common name for the commercial drug Avastin®. It belongs to the antiangiogenic class of drugs. 'Angio' is a term meaning blood; 'genic' comes from the 'genesis', which means new formation or growth. One of the ways this drug works is by interfering with the body's ability to make new blood vessels. As tumors grow they need to supply themselves with blood in order to receive vital nutrients. Bevacizumab is able to reduce the amount of new blood vessels being formed. When a tumor does not get enough blood it cannot grow as fast and sometimes parts or all of a tumor will die. Bevacizumab is approved by the Food and Drug Administration for use in people with colon cancer.

To date, over 7000 patients have been treated in clinical trials with bevacizumab as monotherapy (the only drug being studied) or in combination regimens. Bevacizumab has been studied as monotherapy in renal cell cancer, but also in lung, breast and pancreatic cancers. Recently, bevacizumab has demonstrated a superiority in combination with interferon compared to interferon alone in metastatic renal cell carcinoma.

Studies in animals and in humans suggest that the combination of chemotherapy and an anti-angiogenic agent can be additive or synergistic. In renal cell carcinoma, the combination of ixabepilone and bevacizumab has demonstrated additive anti-tumor effects in animals. This is the rationale for testing the combination in humans. A study is ongoing in patients with metastatic breast cancer to evaluate the same combination.

During the Study

You will receive the premedications ranitidine (Zantac) and diphenhydramine (Benadryl) followed by bevacizumab and ixabepilone intravenously (through a vein). Bevacizumab is given only on day 1 of each cycle, following the premedications, but before the ixabepilone infusion. Sometimes circumstances will not allow Bevacizumab to be admistered on day 1 as planned. If this happens to you it may be given on day 2. Your study doctor will discuss this with you. During cycle one bevacizumab will be infused over 90 minutes. On day 1 of the first cycle the entire infusion time for premedications, bevacizumab and ixabepilone will be at least 3½ hours. On days 2 through 5 the premedications and ixabepilone infusion will be at least 2 hours.

Ixabepilone is infused over a 60-minute period on days 1 through 5 of a 21-28 day cycle. You will receive premedications 1 hour before receiving ixabepilone each day. The premedications are given to prevent an allergic reaction to the ixabepilone infusion. These premedications are ranitidine (Zantac) and diphenhydramine (Benadryl).

During cycle 2 the bevacizumab may be infused over 1 hour, instead of 90 minutes. During cycle 3 the bevacizumab may be given over 30 minutes. These infusion time reductions will depend on the previous cycle and how you tolerated the infusions.

The number of cycles of this combination therapy you receive will depend on your clinical situation. We plan to use x-rays (CT scans) and other studies if necessary, to determine if your tumor is responding to the treatment. These studies will be done after you complete the first 2 cycles, and every 2 cycles thereafter. In making decisions as to whether to continue treatment we will be guided by information from the x-rays and other studies as well as the physical examination and reports from you on how you are tolerating the treatment. The experimental therapy will be stopped if you have worsening of your disease or significant toxicity.

If your tumor grows while you are being treated with bevacizumab and ixabepilone, your experimental treatment will be stopped. In addition, your doctor can stop treatment at any time if in his/her opinion your continued participation would be detrimental to your health or the side effects are unmanageable. You may decide to stop the experimental treatment and withdraw from the study at any time. Upon completion of this study, you may be given the option of participating in additional research protocols that may be appropriate for you, if such protocols exist. If they do not, you will be returned to the care of your referring physician.

Research Biopsies

Tumor biopsies may be done if you agree. The first biopsy is done before the first day of ixabepilone and bevacizumab. The second biopsy is done after the 1st cycle is completed, but before the 2nd cycle has started. This will be approximately 21 days from when you started cycle one. You do not need to have the biopsies done in order to participate in the study. A physician may perform simple biopsies in an examining room using local anesthesia. Other biopsies will be performed in the radiology suite with the help of special equipment such as a CT scan or an ultrasound. These will be performed under local anesthesia by an experienced radiologist. A

needle will be used to obtain the tumor sample. It will pass through your skin and some of the internal tissues between the surface of your skin and the tumor.

This research study involves exposure to radiation from up to 2 CT-directed biopsies. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.26 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

We will use this tissue sample to examine some of the proteins that are important in how cancer cells react to drugs such as ixabepilone and bevacizumab. Part of this sample will be saved and may be used for additional investigations at the conclusion of the study. We want to emphasize that the biopsy will be performed exclusively for research purposes. You will not derive any personal benefit from this. It will help us understand why the drug combination works, if it does, or why it does not work against the cancer if it does not.

Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials_____

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

   Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimens and/or data in new research not included in this consent.

   Yes No Initials_____

Research Blood Tests

You will also have blood collected and analyzed to see if the drugs are having the anticipated effect. In this latter case, we will be looking at your normal cells, to see if the drug has an effect on the normal cells that are circulating in your blood. These blood tests are strictly for research purposes and there is no direct benefit to you from these blood tests. They are required to participate in the study. The research blood will be drawn at the following times during the study:

1. On cycle 1, day 1, prior to receiving either ixabepilone or bevacizumab.
2. On cycle 1, day 5 after the chemotherapy
3. On cycle 2, day 1, prior to receiving either ixabepilone or bevacizumab
4. At the beginning of every other cycle starting with cycle 4.

The amount of blood for research will be 48 ml or slightly more than 3 tablespoons of blood at each of the first 3 time points. Beginning at cycle 4 the amount of research blood will be 24ml (less than 2 tablespoons).

Research Imaging Scans

You will have a special type of MRI scan done before you receive any study medication, again after completing day 5 of cycle 1, and again after completing every 2 cycles. The MRI is called a DCE-MRI. This means a 'dynamic contrast enhanced-magnetic resonance image'. This scan is an MRI of a specific part of your body where a tumor is found. You will lie in an MRI scanner for approximately 30 minutes for this scan to complete. The difference between this DCE-MRI and a routine MRI will not be obvious to you. The difference is in the computer analysis of the images. This scan will be of no direct benefit to you, but it is an important part of the research plan.

Routine Blood Tests for Safety

Prior to each cycle you will have blood tests for safety reasons. These blood tests will check the levels of your white and red blood cells, and your platelets. The blood tests will also check your kidney and liver function. The amount of blood drawn prior to each cycle for safety reasons is 10 ml (2 teaspoons).

After receiving bevacizumab and ixabepilone you will return to your home, but you will need to have blood tests for safety reasons. The first 6 patients on the study will have blood drawn twice a week, during weeks 2 and 3 of their first 2 cycles. If these first 6 patients tolerate their first 2 cycles well, they can reduce the frequency of blood draws to once a week during weeks 2 and 3 of their future cycles. At this point all patients that follow the first 6 patients will have their blood drawn once a week at home during weeks 2 and 3. The amount of blood for safety reasons during weeks 2 and 3 combined will be 28ml (less than 2 tablespoons) for the 1st 6 patients and 8 ml (less than 2 teaspoons) for all others, assuming the first 6 patients tolerate their cycles well. The results of the blood tests will be faxed to the NIH and monitored by the research team.

Blood Pressure Monitoring

You will be asked to measure and record your blood pressure at home. The first 6 patients will measure and record their blood pressure daily during the first two cycles (6weeks). If these first 6 patients tolerate their first two cycles well, they and the following patients on the study can measure and record their blood pressure three times a week. You will be given a blood pressure machine and a diary to record your blood pressure measurements. All patients will be asked to bring their blood pressure records to the NIH for review prior to each cycle.

Phone Calls

The research nurse, or other members of the research team, will call each of the first 6 patients every week during their first 2 cycles to discuss how each patient is feeling, to review the blood pressure readings and any other symptoms they are experiencing. The time of the phone calls will be agreed upon between each patient and the research team. The phone calls should last approximately 5 minutes.

You will be expected to stay in the area for about 7 to 8 days in the first treatment cycle. In subsequent cycles you will need to be in the area for the five days during which the drugs are administered. The amount of drug you receive in the first cycle will be that administered to all patients. In subsequent cycles the dose may be adjusted according to how well your body responds to the chemotherapy and what side effects you have been experiencing. The doses will not be increased, but it may be decreased, if necessary.

Alternative Approaches or Treatments

Because of the type and extent of your tumor, chemotherapy is an option other than surgery or radiation.
Alternative approaches that could be used may include:

1. Radiation treatment that sometimes can control tumor growth in local areas such as lymph nodes, bones, lung and bowel. However, this approach will not effectively treat disease that has spread beyond small areas, as in your case.

2. Surgery that can be used to remove disease from local areas such as lymph nodes, lung and bowel but is not useful for long term control when the disease has spread.

3. Another option is
   - Getting no treatment.
   - Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

4. FDA-approved therapies for kidney cancer including: interleukin-2 (IL-2), sorafenib (Nexavar), sunitinib (Sutent) or temsirolimus (Torisel).

5. Other experimental therapies.

Risks or Discomforts of Participation

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

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

Local anesthesia will be used when biopsies of tumors are performed. The risks associated with these procedures are pain, bleeding and local infection. These risks will be individually explained to you at the time of the procedure.

If biopsies are performed, they may be obtained for either of two reasons: first to confirm your diagnosis or the spread of your tumor and second for experimental purposes including performance of tests on your tumor that may help us understand why it responds or does not respond to treatment. As indicated above, biopsies requiring major surgery (opening the chest or abdomen), or those requiring general anesthesia will only be obtained if necessary for your medical care and will not be obtained for experimental purposes. It is important for you to understand that some of the biopsies of tumor will be performed primarily for experimental purposes, so that we can try to determine why tumors become resistant to chemotherapy. You will not derive any personal benefit from these biopsies.

It will also be necessary to draw blood six to eight times during the first cycle of chemotherapy. These blood draws will be used to determine whether cells in your blood are affected by ixabepilone and bevacizumab. Since chemotherapy (ixabepilone) will result in decreased ability to make new red blood cells, the drawing of blood may increase the risk of anemia and the need for a blood transfusion, or treatment with a drug to increase your red blood cell count.

To receive this experimental therapy you can have a central venous catheter placed. This is a catheter that is placed under the skin of your arm, chest or neck and enters a major vein. This catheter is used for administration of chemotherapy and drawing of blood. There are various types of central catheters. Some are temporary (used for a week and then removed. Some are semi-permanent and are inserted by a surgeon in the operating room using local or general anesthesia. The risks associated with the procedures include pain, bleeding, infection, and development of air in the chest. Air in the chest outside the lung would require temporary placement of a chest tube by the surgeon. Other risks of the catheter include infection and clotting of your veins, which could require removal of the catheter for treatment. These risks will be explained to you in more detail at the time of insertion. You will have the opportunity to learn about all the catheter options and choose the one best for you. If you already have a central catheter, we will use that catheter for your infusions.

Blood tests will be monitored frequently and you will also undergo periodic physical examinations, and be asked to report any side effects you might have experienced. Should any

side effects other than those listed here become apparent during the course of the study, you will be advised of these at the time of study entry, or at any time during the course of the study. We also caution you not to take St. John's Wort (an herb) while receiving Ixabepilone, since this may lead to a drug interaction that could be serious. We also caution you not to drink grapefruit juice while receiving ixabepilone because it may interact with other medications. A complete list of medications that you should not take while participating in this study is included in the following section.
The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

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

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

Here are important points about side effects:

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

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

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

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

Possible Side Effects of Bevacizumab

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• High blood pressure which may cause headache or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving bevacizumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Low white cell count that may increase the risk of infection
- Infection, including collection of pus in the belly or rectum
- Abnormal heartbeat which may cause palpitations or fainting
- Pain in the belly, rectum, chest, joints, muscles, or tumor
- Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up of blood, or blood in urine
- Bleeding from other sites, including the vagina or nose
- Blockage of internal organs which may cause vomiting or inability to pass stool
- Sores in mouth
- Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Delay in healing of wounds or spontaneous opening of wounds
- Weight loss, tiredness, or dizziness
- Damage to the jawbone which may cause loss of teeth
- Headache
- Numbness, tingling, or pain in the fingers or toes
- Hoarseness, stuffy nose, or cough
- Blood clot in limbs or lungs which may cause swelling, pain, or shortness of breath
- Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab, 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, or tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Bleeding in the tumor, brain, belly, or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Ixabepilone toxicity has been extensively studied in animals and in humans. These are the major side effects related to ixabepilone:

COMMON, SOME MAY BE SERIOUS In 100 people receiving ixabepilone, more than 20 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Pain • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ixabepilone, from 4 to 20 may have:
• Abnormal heartbeat • Watering eyes • Constipation • Sores in mouth which may cause difficulty swallowing • Fever • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Swelling and redness of the area of radiation • Loss of appetite, dehydration • Muscle weakness • Dizziness, headache, fainting • Changes in taste • Difficulty talking, sleeping, emptying the bladder • Cough, shortness of breath, hiccups, sore throat • Swelling of the lungs which may cause shortness of breath • Loss of some or all of the nails • Itching, rash • Flushing • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving ixabepilone, 3 or fewer may have:
• Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles • Redness, pain or peeling of palms and soles

Ixabepilone (BMS-247550) is dissolved in a solution that contains a compound called cremophor EL. Because some patients have had allergic reactions to the cremophor EL, you will receive two medications prior to the administration of ixabepilone (BMS-247550), in order to prevent an allergic reaction. The two medications will be diphenhydramine (Benadryl) and ranitidine (Zantac). Although the likelihood a serious side effect will occur from receiving these drugs is low, you should be aware they have potential side effects. Despite receiving premedications, you may still develop an allergic reaction. If that happens the infusion will be stopped and additional diphenhydramine, ranitidine and a third medication, dexamethasone (Decadron), may be added to treat the reaction. This is a rare occurrence.

For diphenhydramine (Benadryl), potential side effects you may experience include:

- Sedation
- Sleepiness
- Dizziness
- Difficulty with coordination
- Abdominal pain
- Dry mouth
- Flushing
- Temporary difficulties passing urine.
- Diphenhydramine may impair your ability to drive and you may need to seek transportation to and from clinic visits.

For ranitidine (Zantac) potential side effects you may experience include:

- Headache
- Fatigue
- Dizziness
- Mild diarrhea
- Temporary confusion
- Rash

For dexamethasone (Decadron) potential side effects you may experience include:

- Increased susceptibility to infection
- Lower values of calcium, potassium, sodium in your blood
- High blood pressure
- Change in mood
- This medication would only be given for a few days during a cycle.

Other medications

Finally, there is evidence that some drugs that you may be taking for other reasons may affect the ability of your body to eliminate Ixabepilone. If you are taking any of these drugs the investigators will discuss the options available including substituting other similar drugs or withholding their administration for a defined period. These drugs include the following:

Antibiotics:

- clarithromycin
- erythromycin
- troleandomycin

Anti-HIV agents:
- delaviridine
- nelfinavir
- amprenavir
- ritonavir
- indinavir
- saquinavir
- lopinavir

Antifungals:
- itraconazole
- ketoconazole
- fluconazole (doses higher than 200 mg/day)
- voriconazole

Calcium channel blockers:
- verapamil
- diltiazem

Miscellaneous:
- amiodarone
- St. John's Wort (herb)

You should not drink grapefruit juice while on this study, because it can interact with other medications.

Pregnancy

Because the drugs in this study can possibly affect an unborn baby and infants, you should not become pregnant or father a baby or breast feed while you are on this study. Also, because bevacizumab and ixabepilone may remain in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of bevacizumab, although the optimal or the maximal time required for drug clearance cannot be precisely predicted

Potential Benefits of Participation

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

Research Subject's Rights

What are the costs of taking part in this study?

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

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor or their agent(s)
- Qualified representatives from the pharmaceutical companies who produce Bevacizumab and Ixabepilone

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

What Happens after This Treatment is completed?

This depends on how you have responded to the experimental therapy. If all evidence of disease has disappeared, we will schedule periodic visits to the Clinical Center for follow-up examination and tests. If the disease does not disappear entirely or if it should recur after having disappeared for a period of time, then you may need further therapy. At that time you will be

given the opportunity of participating in additional research protocols that may be appropriate for you. If no such protocols are available, you will be returned to the care of your local physician. It is conceivable that participation in this study may make you ineligible to participate in certain other research protocols because the requirements for entry onto these protocols may disallow patients who have already been treated with certain drugs or who have had certain side effects from previous treatment.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.
You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

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

Conflict of Interest

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

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

The National Institutes of Health and the research team for this study are using a drug developed by Genentech and Bristol-Myers Squibb through a joint study with your researchers and the companies. The companies also provides financial support for this study.

OTHER PERTINENT INFORMATION

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

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

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

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

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi Madan, M.D.; Building 10, Room3-4460, Telephone: 301- 496-3493. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:	
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. Signature of Adult Patient/ Legal Representative _____ Date _____ Print Name _____	**B. Parent's Permission for Minor Patient.** I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) Signature of Parent(s)/ Guardian _____ Date _____ Print Name _____
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. Signature of Parent(s)/Guardian _____ Date _____ Print Name _____	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 22, 2015 THROUGH JUNE 21, 2016 Signature of Investigator _____ Date _____ Print Name _____	Signature of Witness _____ Date _____ Print Name _____