

**Academic and Community Cancer Research United (ACCRU)**

**Randomized Phase II Study of AB (*nab*-paclitaxel [Abraxane™], Bevacizumab) versus Ipilimumab for Therapy of Unresectable Stage IV Metastatic Malignant Melanoma**

*For any communications regarding this protocol, please contact the person listed on the Protocol Resource page. This is a stand alone document found on the ACCRU website (www/ACCRU.org).*

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Study Co-Chairs: [REDACTED]

Statistician: [REDACTED]

**Drug Availability**

**Commercial Agents:** Ipilimumab

**Drug Company Supplied:** *nab*-paclitaxel (Abraxane™); bevacizumab (Avastin®)

**IND#:** 118184

√ Study contributor(s) not responsible for patient care.

**Research Coordinating Center**

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**Document History**

Pre-activation and Pre-activation Amendment  
Activation ACCRU  
Amendment 1  
Amendment 2  
Amendment 3  
Amendment 4  
Amendment 5

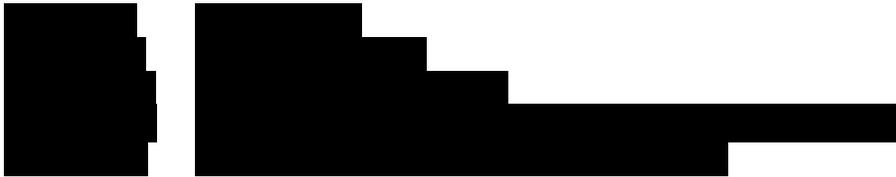
**Effective Date**

July 5, 2013  
October 18, 2013  
November 7, 2014  
April 24, 2015  
May 15, 2015  
April 28, 2017  
October 26, 2018

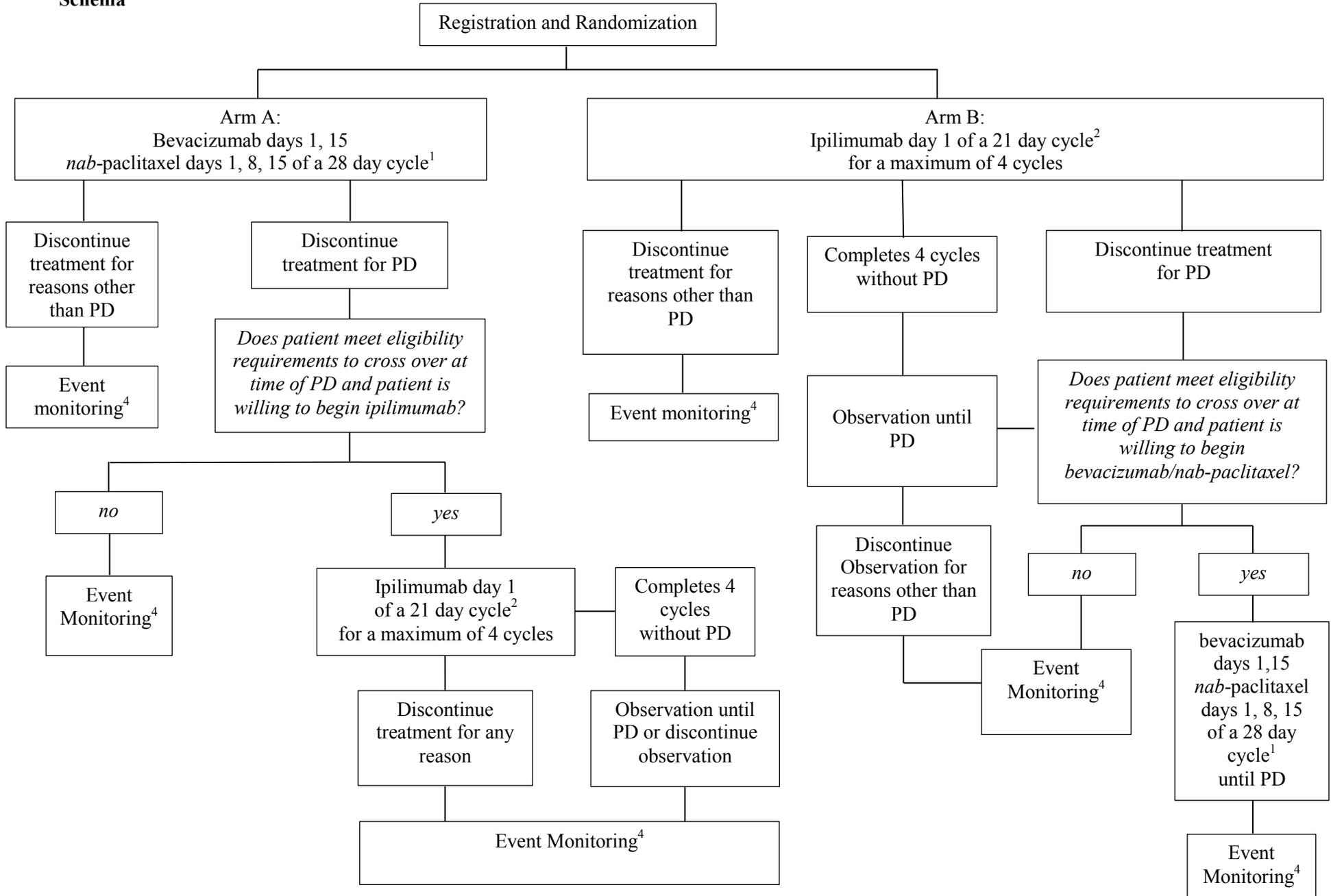
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Schema



If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information

Footnotes follow on next page

<sup>1</sup> Cycle (bevacizumab/*nab*-paclitaxel) = 28 days

<sup>2</sup> Cycle (ipilimumab) = 21 days

<sup>3</sup> **Observation Phase:** Part of the Active Monitoring Phase of a study. The time period following the active treatment phase when the participant continues to undergo evaluations and complete specimen submission in compliance with the Test Schedule. (see Sections 4.2 and 4.3)

<sup>4</sup> **Event Monitoring:** Not part of the Active Monitoring phase of a study. During the Event Monitoring Phase of the study, consenting ACCRU institution are being asked to provide notification as to whether the participant has progressed, developed a new primary, and/or died. Participants are not be required to return to their registering site to undergo any study related medical examinations or specimen collections. All treatment decisions are in the hands of the participant and their medical team. (see Section 13.0)

<p>Generic name: Ipilimumab                  Brand name(s): Yervoy™                  ACCRU Abbreviation: IPILIMUMAB                  Availability: Commercial</p>	<p>Generic name: Bevacizumab                  Brand name(s): Avastin®                  ACCRU Abbreviation: AVASTN                  Availability: ACCRU Research Coordinating Pharmacy</p>	<p>Generic name: <i>nab</i>-paclitaxel                  Brand name(s): Abraxane™                  ACCRU Abbreviation: ABI007                  Availability: ACCRU Research Coordinating Pharmacy</p>
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## 1.0 Background

Metastatic malignant melanoma remains an incurable condition with median OS of 6-10 months and a median progression free survival (PFS) of 40-60 days[1]. Effective systemic therapy capable of meaningful prolongation of OS in this patient population has remained elusive. However, a phase III clinical trial of patients with previously treated unresectable metastatic melanoma found that ipilimumab (IPI, anti-CTLA-4 blocking antibody) significantly improved OS (**OS = 10 months**) over a gp100 peptide vaccine (OS = 6.4 months). Progression-free survival (PFS) was similar between the two treatment arms with **median PFS of 2.86 months** for IPI and 2.76 months for the peptide vaccine[2]. The most common of adverse events with IPI involved auto-immune reactions involving the colon, liver, skin, endocrine system and nervous systems. Management of immune-mediated adverse events included discontinuation of and initiation of high dose corticosteroids. In March 2011, based on these findings, the Food and Drug Administration (FDA) approved IPI (Yervoy<sup>®</sup>) for the treatment of unresectable or metastatic melanoma at a dose of 3mg/kg administered every 3 weeks for a total of 4 doses (any “line” therapy). Higher doses of IPI or maintenance therapy were not approved for use by the FDA. Thus, IPI is now considered the standard of care, any “line” therapy for patients with metastatic melanoma. Similarly, in August of 2011, the FDA approved the use of vemurafenib (PLX-4302) for use in the therapy of patients with metastatic malignant melanoma exhibiting a specific mutation in the BRAF gene (V600E). The drug was approved on the strength of a prematurely terminated phase 3 clinical trial (BRIM-3) comparing the efficacy of vemurafenib (VEM) vs dacarbazine (DTIC) in this patient population[3]. Due to significant improvement of PFS in the VEM arm (**5.3 months vs 1.6 months**), the study was closed and VEM was approved for this indication (Zelboraf<sup>®</sup>). Thus, in 2012 we now have two new approved agents for the treatment of advanced melanoma, in addition to DTIC and interleukin-2. However, despite these advances, nearly all patients with metastatic melanoma still progress on therapy and ultimately succumb to their disease. The need for effective therapy remains acute.

In 2011, we completed a multicenter randomized Phase 2 clinical trial in the North Central Cancer Treatment Group (NCCTG, protocol N0775) in which chemotherapy naïve patients with metastatic melanoma were treated with either a combination of *nab*-paclitaxel (Abraxane<sup>™</sup>, ABX, ABI007), bevacizumab and carboplatin (ABC regimen) or temozolomide and bevacizumab (TB regimen). The study was not designed to compare the clinical efficacy of the two treatments; each arm was compared to historic control rates with the intent of gaining insight into a potential superior chemotherapy back-bone for bevacizumab therapy combinations in metastatic melanoma[4]. The study accrued 51 patients to the ABC regimen and 41 patients to the TB regimen. The regimens yielded **median PFS/OS of 6.7/13.9 months for ABC** and 3.8/12.3 for TB. These results compare favorably to two other of our multicenter Phase 2 NCCTG trials in the same patient population (N047A and N057E). For patients with stage IV melanoma treated with a 28 day cycle of paclitaxel (Taxol<sup>®</sup>, 80mg/m<sup>2</sup> days 1, 8 and 15), bevacizumab (10mg/kg days 1 and 15) and carboplatin (AUC 6 on day 1) until tumor progression on N047A, the median PFS was 6 months and the median OS was 12 months[5]. In protocol N057E, two phase 2 clinical trials were conducted concurrently examining the antitumor activity of a 28 day cycle of *nab*-paclitaxel (100mg/m<sup>2</sup> days 1, 8 and 15) and carboplatin (AUC 2 on days 1, 8 and 15) administered until progression in chemotherapy naïve and previously chemotherapy treated patients respectively[6]. Both patient cohorts were similar in terms of median PFS survival (approximately 4 months) and median OS (approximately 11 months). Thus, in the phase 2 clinical trial setting, the combination of a taxane and carboplatin was found to provide clinical benefit in patients with malignant melanoma, and the addition of bevacizumab seemed to add further improvements in both PFS and OS. Our best result was achieved with *nab*-paclitaxel as the “taxane” element of the three drug combination.

Recently presented results by Spitler et al, (ASCO 2011) testing the utility of the combination of *nab*-paclitaxel and bevacizumab (without carboplatin, AB regimen) at doses of 150mg/m<sup>2</sup> days 1, 8 and 15, and 10mg/kg on days 1 and 15 respectively, in chemotherapy naïve patients with metastatic melanoma (50 patients) revealed a median **PFS of 7.6 months and OS of 16.8 months**. Main

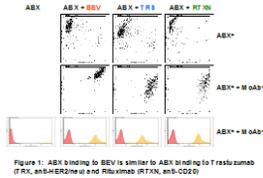
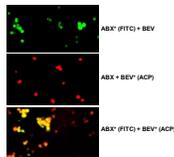


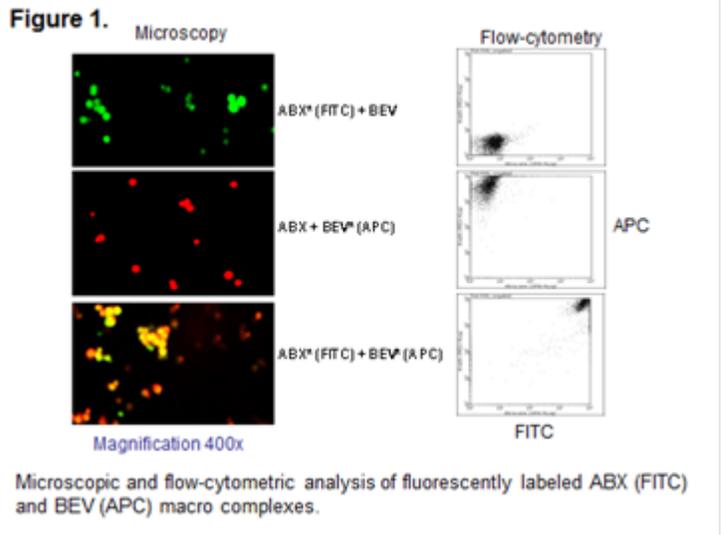
Figure 1: ABX binding to BEV is similar to ABX binding to Trastuzumab (TRS), anti-HER2/neu and Rituximab (RTX), anti-CD20

severe toxicities (grade 3 only, no grade 4) were: neutropenia (10 of 26), neuropathy (7 of 26) mucositis (4 of 26), fatigue (3 of 26), and proteinuria and hand/foot syndrome in 1 of 26 patients respectively. The similarity (and small advantage) in the PFS/OS of this combination relative to our ABC regimen (above), as well as its superiority to the paclitaxel/carboplatin/bevacizumab regimen of N047A (PFS = 6 months, OS = 12 months), suggested a potential synergy/interaction between *nab*-

paclitaxel and bevacizumab. As the only difference between the paclitaxel preparations was the vehicle (albumin nanoparticle versus Cremophor EL), we postulated that there could exist a here-to-for unrealized pharmacokinetic interaction between the albumin nanoparticle of *nab*-paclitaxel and the monoclonal antibody of bevacizumab. With that in mind we conducted a series of experiments attempting to assess whether or not *nab*-paclitaxel could interact with bevacizumab in



vitro. To our surprise (Fig. 1,



*nab*-paclitaxel /bevacizumab column) in vitro mixing of *nab*-paclitaxel and bevacizumab resulted in the creation of macromolecular complexes. In these experiments clinical grade *nab*-paclitaxel was fluorescently labeled and mixed in vitro (room temperature) with clinical grade (fluorescently labeled) bevacizumab (bevacizumab), trastuzumab (TRS) or rituximab (RTX). These mixtures resulted in micro-complexes (approximately 1-2

microns) that were analyzed via flow-cytometry and demonstrate that all nano-particles (*nab*-paclitaxel, single fluorescence) indeed bind the fluorescent antibodies (dual fluorescence of the mixture). This *nab*-paclitaxel interaction with bevacizumab

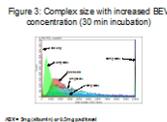
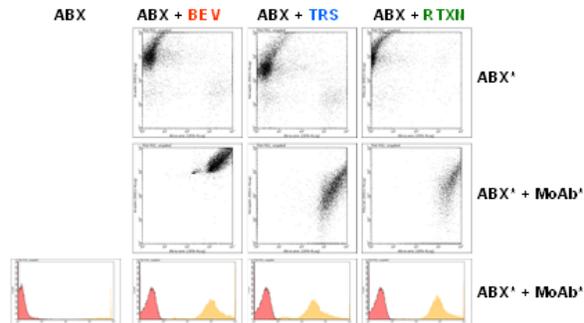


Figure 3: Complex size with increased BEV concentration (30 min incubation)

was not only a feature of bevacizumab, but, also could be identified in combinations of trastuzumab (Herceptin®) and rituximab (Rituxan®). Microscopic examination of these particles (*nab*-paclitaxel + bevacizumab

Figure 9.

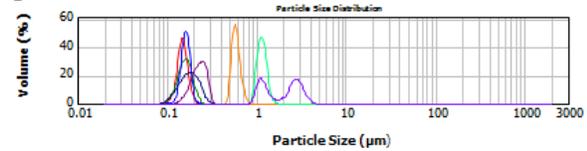


Flow cytometric analysis of macomolecular complexes following fluorescently labeled ABX (ABX\*) incubation with BEV exhibit similar binding affinity to other fluorescently labeled monoclonal antibodies (MoAb\*), trastuzumab (TRS) or rituximab (RTXN).

was not only a feature of bevacizumab, but, also could be identified in combinations of trastuzumab (Herceptin®) and rituximab (Rituxan®). Microscopic examination of these particles (*nab*-paclitaxel + bevacizumab

only) confirms this impression (**Fig. 2**). The size of the *nab*-paclitaxel/bevacizumab complexes can be varied dependent on the relative concentrations of each component (**Fig. 3**). Additional in vitro data demonstrate that the binding of *nab*-paclitaxel and bevacizumab can be inhibited by normal plasma as well as soluble albumin, the complexes appear to be stable at room temperature for at least 4 hours, and that upon incubation in fresh human plasma at 37°C/5% CO<sub>2</sub>, their half-life is on the order of 30 seconds (data not shown). All of these preliminary data suggest that one potential explanation for the therapeutic advantage of the replacement of *nab*-paclitaxel for paclitaxel in combination with bevacizumab could be there result of a pharmacokinetic interaction taking place during the infusion of *nab*-paclitaxel that immediately follows the infusion of bevacizumab in the two cited trial regimens of ABC and AB (██████████). Due to the rapid saturation of the bevacizumab (antibody) binding sites on *nab*-paclitaxel by normal plasma, the efficiency of this complex formation during sequential infusions of the agents into patients is likely very small. However, it is conceivable that the higher concentration of *nab*-paclitaxel used in Dr. Spitler's study (150mg/m<sup>2</sup>) vs ours (100 or 80mg/m<sup>2</sup>) could have created the complexing advantage postulated by these laboratory studies.

**Figure 3.**



ABX (mg/ml)	BEV (mg/ml)	d (0.1) um	d (0.5) um	d (0.9) um
10	0	0.125	0.146	0.174
10	2	0.122	0.157	0.196
10	4	0.138	0.159	0.182
10	6	0.124	0.174	0.235
10	8	0.171	0.226	0.278
10	10	0.516	0.577	0.67
10	15	0.981	1.129	1.31
10	25	1.036	2.166	3.233

Absolute size distributions of nanoAB as a function of increasing concentration of BEV (mg/mL) with fixed concentration of ABX (10 mg/mL). Table reflects fractional distribution (e.g. 0.1) of sizes of nano particles.

Based on these data, it appears that both the ABC regimen (*nab*-paclitaxel/bevacizumab/carboplatin) and *nab*-paclitaxel/bevacizumab (AB) offer therapeutic results in chemotherapy naïve patients with metastatic melanoma that are superior to those of ipilimumab therapy, the currently FDA approved agent for the treatment of patients with metastatic melanoma, with heavy clinical use in patients who do not harbor the BRAF V600E mutation. The small PFS/OS advantage of the AB over the ABC regimen may be the result of this unexpected pharmacokinetic interaction of bevacizumab and the higher dose of *nab*-paclitaxel (150mg/m<sup>2</sup> vs 100mg/m<sup>2</sup>). Additionally, the AB regimen appears significantly less toxic. **Therefore, in the current study, we propose to compare the clinical efficacy of the AB regimen (*nab*-paclitaxel 150mg/m<sup>2</sup> days 1, 8 and 15; bevacizumab = 10mg/kg, days 1 and 15) in patients undergoing therapy for metastatic melanoma and compare to the current standard, ipilimumab.** The AB regimen will be uniformly administered with bevacizumab infusion preceding the infusion of *nab*-paclitaxel in all study patients. Study participants will be stratified based on M sub-stage (M1c vs other), BRAF 600 mutation present (yes vs. not or metastatic melanoma is of uveal origin), and prior treatment in the metastatic setting (yes vs. no).

The primary end aim of this study is to assess whether there is a 33% increase in PFS with AB relative to IPI. At the time of first disease progression, patients will cross over to the other treatment regimen, Correlative pharmacokinetic (testing the possibility of creation of the *nab*-paclitaxel/bevacizumab complexes, and persistence of paclitaxel in circulation), and pharmacodynamic (effects of therapy on parameters of immunity and angiogenesis), will also be performed. The former, in combination with ongoing pre-clinical studies, will provide the foundation for a future study of pre-infusion mixing of *nab*-paclitaxel and bevacizumab, creating *nab*-paclitaxel/bevacizumab complexes prior to infusion into patients and an introduction of a novel therapeutic platform in which the albumin nanoparticle of *nab*-paclitaxel may serve as the

chemotherapeutic carrier delivering concentrated chemotherapeutics to the sites of cancer directed by complexed monoclonal therapeutic antibodies (at least bevacizumab and potentially trastuzumab, and rituximab). Analysis of the immunological and anti-angiogenic outcomes of AB and IPI therapy will yield critical insights into potential mechanisms of action and lay the foundation for future combinatorial strategies us AB as the chemotherapy “back-bone” of non-BRAF mutated metastatic melanoma (concurrent or sequential therapy concepts).

## 2.0 Goals

### 2.1 Primary Goal

- 2.11 To assess whether the combination *nab*-paclitaxel and bevacizumab (AB) prolongs progression-free status relative to ipilimumab as a treatment in patients with unresectable stage IV melanoma

### 2.2 Secondary Goals

- 2.21 To estimate the hazard of death among those randomized to AB then ipilimumab relative to those randomized to ipilimumab then AB as treatment in patients with unresectable stage IV melanoma.
- 2.22 To assess whether tumor response rate (as determined by RECIST criteria 1.1) differs with respect to 1<sup>st</sup> treatment course.
- 2.23 To estimate whether the tumor response rate differs with respect to 2<sup>nd</sup> treatment course for those who progressed during their first treatment course.
- 2.24 To further examine the safety profile of each of these regimens.

### 2.3 Correlative Goals

- 2.31 **For patients accrued at Mayo Clinic in Rochester, MN ONLY (mandatory):** To examine the pharmacokinetics of *nab*-paclitaxel when combined with bevacizumab therapy
- 2.32 **For patients accrued at Mayo Clinic in Rochester, MN ONLY (mandatory):** To examine pharmacodynamic changes of blood-derived parameters (biomarkers) of angiogenesis and immunity as a function of therapy.
- 2.33 **All sites (optional):** To examine whether changes in serum biomarkers are also seen in the tumor.

### 3.0 Patient Eligibility

#### 3.1 Inclusion criteria

- 3.11 Histologic or cytologic proof of surgically unresectable stage IV malignant melanoma - including that of uveal and mucosal origin

Note: Biopsy can be of locoregional disease in setting of clinically evident stage IV disease. A biopsy of the primary tumor alone does not fulfill this requirement.

- 3.12 No more than 2 prior courses of systemic therapy for metastatic melanoma.

- 3.13 For patients with metastatic melanoma **not** of uveal origin, BRAF V600 mutation determination using a CLIA-approved testing method on metastatic tumor tissue.

NOTE: Patients with metastatic melanoma of uveal origin **do not need** to have formal BRAF testing due to low probability of a BRAF V600 mutation in their metastatic tumor.

- 3.14 Measurable disease defined in Section 11.2.

**Note:** Disease that is measurable by physical examination only is not eligible.

- 3.15 Life expectancy of  $\geq 4$  months.

- 3.16 Age  $\geq 18$  years.

- 3.17 ECOG performance status (PS) 0 or 1.

- 3.18 The following laboratory values obtained  $\leq 14$  days prior to registration/randomization:

- Absolute neutrophil count  $\geq 1500/\text{mL}$
- Platelet count  $\geq 100,000 \times 10^9/\text{L}$
- Hemoglobin  $\geq 9 \text{ g/dL}$  (patients may be transfused to meet this requirement)
- Creatinine  $\leq 1.5 \times \text{ULN}$ . Institutional norms are acceptable.
- Total bilirubin  $\leq 1.5 \text{ mg/dL}$  (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
- SGOT (AST)  $\leq 2.5 \times \text{ULN}$  and SGPT (ALT)  $\leq 2.5 \times \text{ULN}$
- Alkaline phosphatase  $\leq 2.5 \times \text{ULN}$ . If bone metastasis is present in the absence of liver metastasis then  $\leq 5 \times \text{ULN}$
- Urine dipstick for proteinuria  $< 2+$  (patients discovered to have  $\geq 2+$  proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate  $\leq 1 \text{ g}$  of protein in 24 hours to be eligible).

- 3.19a Negative serum pregnancy test done  $\leq 7$  days prior to registration/randomization, for women of childbearing potential only.

**Note:**

**Females:** Adequate contraception must be used by both patient and partner while receiving study drug and for 12 weeks after the last dose of study drug.

**Males:** Adequate contraception must be used by both patient and partner while receiving study drug. Men who have a partner of childbearing age should also avoid fathering a child for 6 months after the last dose of study drug.

- 3.19b Ability to understand and the willingness to sign a written informed consent document.
- 3.19c Mayo Rochester patients only: Willingness to provide mandatory blood samples for research purposes (see Section 14.0).
- 3.2 Exclusion Criteria
- 3.21 Brain metastases per MRI or CT.
- Note:** Patients who have had therapy for brain metastasis (i.e., surgical resection, whole brain radiation, or SRS even if stable) are not eligible.
- 3.22 Other investigational agents  $\leq$  4 weeks prior to registration/ randomization.
- 3.23 Anti-cancer therapy (including immunotherapy)  $\leq$  4 weeks prior to registration/randomization. Exception: adjuvant Leukine®  $\leq$  14 days prior to registration/randomization.
- 3.24 Prior treatment in the adjuvant or metastatic setting with any of the following:
- agents disrupting VEGF activity or targeting VEGFR;
  - ipilimumab;
  - or taxane based chemotherapy regimens (including paclitaxel, docetaxel, cabizataxel or *nab*-paclitaxel).
- 3.25 Major surgical procedure, open biopsy, or significant traumatic injury  $\leq$ 4 weeks prior to registration/randomization. (Port-a-cath placement does not count as a major surgical procedure and patients can be enrolled at any time after placement).
- 3.26 Fine needle aspirations or core biopsies  $\leq$ 7 days prior to registration/ randomization.
- 3.27 Planned/or anticipated major surgical procedure during the course of the study.
- 3.28 Other medical conditions including but not limited to:
- History of liver disease such as cirrhosis, chronic active hepatitis, chronic persistent hepatitis or hepatitis B or C
  - Active infection requiring parenteral antibiotics
  - Poorly controlled high blood pressure ( $\geq$ 150 mm Hg systolic and/or 100 mmHg diastolic) despite treatment.

- New York Heart Association class II-IV congestive heart failure (available on ACCRU web site at <https://ACCRU.mayo.edu/ACCRU/forms/NonProtocolSpecificForms>).
  - Serious cardiac arrhythmia requiring medication.
  - Myocardial infarction or unstable angina  $\leq 6$  months prior to registration/randomization.
  - Clinically significant peripheral vascular disease.
  - Deep venous thrombosis or pulmonary embolus  $\leq 1$  year of registration/randomization
  - Ongoing need for full-dose oral or parenteral anticoagulation.
  - Ongoing anti-platelet treatment other than low-dose aspirin (i.e., aspirin 81 mg by mouth daily).
  - Active bleeding or pathological conditions that carry high risk of bleeding (e.g., known esophageal varices, etc.).
  - Serious, non-healing wound (including wounds healing by secondary intention), ulcer or bone fracture.
  - History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess  $\leq 6$  months prior to registration/randomization.
  - History of CNS disease (e.g., vascular abnormalities, etc.), clinically significant stroke or TIA  $\leq 6$  months prior to registration/randomization, seizures not controlled with standard medical therapy.
  - Radiographically documented tumor invading major blood vessels.
  - History of hypertensive crisis or hypertensive encephalopathy.
- 3.29a Any of the following as this regimen may be harmful to a developing fetus or nursing child:
- Pregnant women.
  - Nursing women.
  - Men and women of reproductive potential who are not using effective birth control methods.
- Note:** Women of childbearing potential must have a negative serum pregnancy test  $\leq 7$  days prior to registration/randomization. Adequate contraception must be used while receiving study drug and for 12 weeks after the last dose of study drug, by both women and men and by both patient and partner.
- Men who have a partner of childbearing potential should also avoid fathering a child for 6 months after the last dose of study drug.
- 3.29b Existence of peripheral sensory neuropathy  $\geq$  grade 2 (from any cause).
- 3.29c History of other malignancy  $\leq 5$  years with the exception of basal cell or squamous cell carcinoma of the skin, treated with local resection only, or carcinoma in situ (e.g. of the cervix, breast, prostate, etc.).
- 3.29d Radiation therapy (other than palliative)  $\leq 2$  weeks prior to randomization. **Note:** Patients who have had  $>25\%$  of their functional bone marrow irradiated are not eligible for this trial.
- 3.29e Active or recent history of hemoptysis ( $\geq \frac{1}{2}$  teaspoon of bright red blood per episode)  $\leq 30$  days prior to registration/randomization.

- 3.29f Known hypersensitivity to any of the components of ipilimumab, bevacizumab, or *nab*-paclitaxel.
- 3.29g History of inflammatory bowel disease (e.g., Crohn's, ulcerative colitis) - Note patients with irritable bowel syndrome are eligible.
- 3.29h Diagnosis of autoimmune disease (i.e., rheumatoid arthritis, scleroderma, SLE, autoimmune vasculitis, Guillain-Barre Syndrome, etc.), regardless if patient is currently receiving treatment at time of registration/randomization.
- 3.29i Systemic corticosteroids use  $\leq 2$  weeks, regardless of indication.

**Note:** Patients who are on inhaled corticosteroids are eligible.

#### 4.0 Test Schedule

##### 4.1 Tests and procedure prior to registration/randomization Arm A & B

Tests and Procedures	$\leq 14$ days prior to registration/randomization
History, exam, wt., ECOG Performance Status (PS)	X
Serum Pregnancy Test	X <sup>1</sup>
Height	X
ANC, WBC, PLT, Hgb, Absolute monocyte count (AMC), absolute lymphocyte count (ALC), eosinophils	X
Chemistry group SGOT (AST), ALT, total bilirubin, Alk Phos, Creatinine, potassium, sodium, LDH	X
TSH	X
Blood Pressure	X
Urinalysis for proteinuria	X <sup>2</sup>
Brain MRI (or CT with contrast of the head if MRI cannot be performed)	X <sup>3</sup>
AE assessment	X
Tumor Measurement/evaluation	X <sup>3,4</sup>
BRAF V600 analysis of metastatic melanoma	X <sup>5</sup>
Optional research tissue sample <sup>6,R</sup>	X

1. For women of childbearing potential only (must be done  $\leq 7$  days prior to registration).
2. All patients must have a urinalysis  $\leq 48$  hour prior to Day 1 of the cycle. For treatment modifications for bevacizumab based on proteinuria, see Section 8.4.
3.  $\leq 28$  days prior to registration/randomization.
4. See Appendices II and III for imaging guidelines and image submission instructions. Excluding brain MRI and/or CT scan of the head with contrast, images should represent the entire radiologic assessment for the tumor.
5. BRAF V600 metastatic tumor tissue typing may be done at any time prior to study registration but must be done on a site of metastasis, not the primary lesion (patients with uveal melanoma are not required to undergo formal testing).
6.  $\leq 30$  days prior to registration/randomization- see Section 17.0 for additional details
- R. Research funded.

**4.2 Arm A: Bevacizumab in combination with *nab*-paclitaxel (AB) followed by ipilimumab after progression**

Tests and Procedures*	Bevacizumab and <i>nab</i> -paclitaxel Treatment phase				Ipilimumab Treatment and Observation phase			
	Prior to first dose of nab-Pac/BEV Mayo Clinic-R patients only	Prior to each cycle of treatment <sup>1</sup>	Day 8 & 15 of each cycle of treatment	At time of progression	Prior to first dose of Ipilimumab Mayo Clinic-R patients only	Prior to each dose of Ipilimumab <sup>2</sup>	Observation until PD (every 8 weeks after completion of 4 cycles of ipilimumab)	At time of Progression
Physical exam, wt., ECOG PS		X		X		X	X	X
ANC, AMC, ALC, WBC, PLT, Hgb		X	X <sup>3</sup>	X		X	X	X
Chemistry group ( AST, ALT, total bili, Alk Phos, Creatinine, potassium, sodium, LDH)		X		X		X	X	X
Blood Pressure		X <sup>4</sup>	X <sup>4</sup>	X				
TSH						X	X	X
Urinalysis for proteinuria		X <sup>5</sup>		X				
Mandatory research blood samples <sup>R</sup>	X <sup>6</sup>				X <sup>6</sup>			
AE assessment		X		X		X	X	X
Tumor Measurement/evaluation <sup>7</sup>		X <sup>8</sup>		X <sup>7</sup>		X <sup>9, 10, 11</sup>	X	X <sup>7</sup>

1. If tests have been done  $\leq 21$  days prior to registration/randomization, they need not be repeated for the first cycle.
2. If tests have been done  $\leq 21$  days prior to cycle 1 day 1 of **ipilimumab treatment** they need not be repeated for the first cycle of **ipilimumab treatment**.
3. May be done up to 48 hours prior to days 1, 8, 15 of each cycle of treatment.
4. Blood pressure must be measured weekly for cycle 1 and then before each bevacizumab infusion (i.e., on days 1 and 15). Though the primary oncologist is expected to see the patient only on day 1 of every cycle, if blood pressure is found to be elevated (i.e., systolic blood pressure  $\geq 150$  mmHg and/or diastolic blood pressure  $\geq 100$  mmHg) on day 15 during the first cycle or on day 15 during subsequent cycles, the treating physician should be notified.
5. All patients must have urinalysis  $\leq 48$  hours prior to day 1 of the cycle. For treatment modifications for bevacizumab based on proteinuria, see Section 8.6.
6. **For patients accrued at Mayo Clinic in Rochester, Minn. ONLY:** See Section 14.0 for collection, preparation, and delivery instructions.
7. See Appendix II for imaging guidelines and Appendix III for image submission process. Images should be submitted on CD: (1) following progression on AB; (2) following progression on IpI, and (3) at the end of protocol treatment for reasons other than progression. Excluding brain MRI and/or CT scan of the head with contrast, images should represent the entire radiologic assessment for the tumor.
8. Tumor measurements during bevacizumab and *nab*-paclitaxel treatment phase are to be taken: prior to cycle 4 (i.e., approximately week 12) and then prior to every other cycle (i.e., prior to cycles 6, 8, etc.) until progression (PD). EXCEPTION: If a patient is experiencing a complete tumor response at the year 3 post-randomization time point, tumor measurement schedule can be modified so that tumor measurements are taken every 6 months until disease progression.
9. Tumor measurements must be repeated prior to the start of ipilimumab treatment phase if more than 28 days have elapsed since last tumor measurements were taken.
10. Patients who progress on Bevacizumab and *nab*-paclitaxel and who wish to crossover to Ipilimumab therapy must undergo an assessment for brain metastases with an MRI (if MRI not possible due to contraindications, contrast CT will be acceptable)
11. Tumor measurements during ipilimumab treatment phase: The first scan after patients have initiated therapy with ipilimumab should be taken approximately 3 weeks after the fourth dose of ipilimumab (i.e., approximately week 12 after start of ipilimumab) and then every 8 weeks until disease progression. EXCEPTION: If a patient is experiencing a complete tumor response at the year 3 post-crossover time point, tumor measurement schedule can be modified so that tumor measurements are taken every 6 months until disease progression.
- R. Research funded.

**4.3 Arm B: Ipilimumab followed by *nab*-paclitaxel and bevacizumab (AB) after progression**

Tests and Procedures	Ipilimumab Treatment and Observation Phase				Bevacizumab and <i>nab</i> -paclitaxel Treatment phase				
	Prior to first dose of Ipilimumab Mayo Clinic- R patients only	Prior to each cycle of treatment <sup>1</sup>	Observation until PD (every 8 weeks after completion of 4 cycles of ipilimumab)	At time of progression	Prior to first dose of nab-Pac/BEV Mayo Clinic-R patients only	Prior to each subsequent cycle of AB	Day 8 & 15 of each cycle of treatment	At time of progression	AE Monitoring (4 weeks after completion of <i>nab</i> -paclitaxel/ BEV)
Physical exam, wt., ECOG PS		X	X	X		X		X	
ANC, AMC,ALC, WBC, PLT, Hgb		X	X	X		X <sup>2</sup>	X <sup>3</sup>	X	
Chemistry group (AST, ALT, total bili, Alk Phos, Creatinine, potassium, sodium, LDH)		X	X	X		X		X	
Blood Pressure						X <sup>4</sup>	X <sup>4</sup>		
TSH		X	X	X					
Urinalysis for proteinuria						X <sup>5</sup>			
Mandatory research blood samples <sup>R</sup>	X <sup>6</sup>				X <sup>6</sup>				
AE assessment		X	X	X		X		X	X
Tumor Measurement/ Evaluation <sup>7</sup>		X <sup>8</sup>	X <sup>8</sup>	X <sup>7</sup>		X <sup>9, 10,11</sup>		X <sup>7</sup>	

1. If tests have been done  $\leq 21$  days prior to registration/randomization they need not be repeated for the first cycle.
2. If tests have been done  $\leq 21$  days prior to cycle 1 day 1 of **bevacizumab and nab-paclitaxel treatment** they need not be repeated for the first cycle of **bevacizumab and nab-paclitaxel treatment**.
3. May be done up to 48 hours prior to treatment days 1, 8, 15.
4. Blood pressure must be measured before each bevacizumab infusion (e.g. on days 1 and 15). Though the primary oncologist is expected to see the patient only on day 1 of every cycle, if blood pressure is found to be elevated (i.e., systolic blood pressure  $\geq 150$  mmHg and/or diastolic blood pressure  $\geq 100$  mmHg) on day 15 during the first cycle or on day 15 during subsequent cycles, the treating physician should be notified.
5. All patients must have urinalysis  $\leq 48$  hours prior to day 1 of the cycle. For treatment modifications for bevacizumab based on proteinuria, see Section 8.4.
6. **For patients accrued at Mayo Clinic in Rochester, Minn. ONLY:** See section 14.0 for collection, preparation, and delivery instructions.
7. See Appendix II for imaging guidelines and Appendix III for image submission process. Images taken during the study should be submitted on CD: (1) following progression on AB; (2) following progression on IpI, and (3) at end of protocol treatment for reasons other than progression. Excluding brain MRI and/or CT scan of the head with contrast, images should represent the entire radiologic assessment for the tumor.
8. Tumor measurements during ipilimumab treatment phase: The first scan after patients have initiated therapy with ipilimumab should be taken approximately 3 weeks after the fourth dose of ipilimumab (i.e., approximately week 12 after start of ipilimumab) and then every 8 weeks thereafter until progression.  
**EXCEPTION:** If a patient is experiencing a complete tumor response at the year 3 post randomization time point, tumor measurement schedule can be modified so that tumor measurements are taken every 6 months until disease progression
9. Tumor measurements must be repeated prior to the start of bevacizumab and nab-paclitaxel treatment phase if more than 28 days have elapsed since last tumor measurements were taken.
10. Patients who progress on Ipilimumab and who wish to crossover to bevacizumab and nab-paclitaxel therapy must undergo an assessment for brain metastases with an MRI ((if MRI not possible due to contraindications, contrast CT will be acceptable)
11. Tumor measurements after initiating bevacizumab and nab-paclitaxel treatment phase are to be taken prior to the fourth cycle of AB (i.e., approximately week 12 after start of AB) and then prior to every other cycle (i.e., prior to cycles 6, 8, etc.) until progression.  
**EXCEPTION:** If a patient is experiencing a complete tumor response at the year 3 post cross-over time point, tumor measurement schedule can be modified so that tumor measurements are taken every 6 months until disease progression.
- R. Research funded.

## 5.0 Stratification Factors

- 5.1 Metastatic disease sub-stage (per AJCC v7): M1a/M1b vs. M1c.
- 5.2 BRAF V600 mutation: present vs. not present or metastatic melanoma is of uveal origin
- 5.3 Previous treatment for metastatic disease: Yes vs. no.

## 6.0 Registration/Randomization Procedures

### 6.1 Registration Procedures

- 6.11 To register a patient, access the ACCRU web page at [REDACTED] and under Remote Registration, click on “Registration/randomization.” The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact **information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).**

The instructions for the registration/randomization application are available by using the Help button.

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [REDACTED]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

### 6.12 Correlative Research

**Mayo Rochester patients only:** A mandatory correlative research component using blood samples is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 14.0).

**All patients:** An optional correlative research component using a tissue sample is part of this study. There will be an option to select if the patient is to be registered onto this component (see Section 17.0).

Patient has/has not given permission to give his/her tissue sample for research testing.

- 6.13 Documentation of IRB approval must be on file in the ACCRU Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submitting of annual IRB approvals is required until the study has been closed through your IRB.

- 6.14 Prior to accepting the registration, the registration/randomization application will verify the following:
- IRB approval at the registering institution
  - Patient eligibility
  - Existence of a signed consent form
  - Existence of a signed authorization for use and disclosure of protected health information (*U.S.A. institutions only*)

At the time of registration/randomization, the following will be recorded:

- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
  - Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
  - Patient has/has not given permission for ACCRU to give his/her blood sample(s) to outside researchers.
  - Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
  - Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
  - Patient has/has not given permission for ACCRU to give his/her tissue sample(s) to outside researchers.
- 6.15 Treatment cannot begin prior to registration/randomization and must begin  $\leq 7$  days after registration/randomization.
- 6.16 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.17 All required baseline symptoms (see Section 10.5) must be documented and graded.
- 6.18 Treatment on this protocol must commence at the accruing membership under the supervision of an ACCRU member physician.
- 6.19a Study drug is available on site.
- 6.19b Blood draw kit is available on site.

## 6.2 Randomization Procedures

- 6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.
- 6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following

treatment groups using the Pocock and Simon<sup>9</sup> d dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

- Arm A: Bevacizumab + *nab*-paclitaxel (AB) followed by ipilimumab
- Arm B: Ipilimumab followed by AB

## 7.0 Protocol Treatment

### 7.1 Bevacizumab/*nab*-paclitaxel

One treatment cycle = 28 days ( $\pm 2$  days)

Agent*	Dose	Schedule	Route	Retreatment
Bevacizumab	10mg/kg	Days 1 and 15	IV over 90 minutes**	Every 28 days ( $\pm 2$ days) until progression
<i>nab</i> -paclitaxel	150mg/m <sup>2</sup>	Days 1, 8, 15	IV over 30 minutes***	

\* Drugs should be administered in the order listed above. **ALWAYS INFUSE BEVACIZUMAB FIRST.**

\*\* Subsequent infusions of bevacizumab may be administered over 60 minutes if tolerated. If tolerated over 60 minutes, may administer over 30 minutes.

\*\*\* Following administration of *nab*-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.

### 7.2 Ipilimumab

One treatment cycle = 21 days ( $\pm 2$  days)

Drug	Dose	Schedule	Route	Retreatment
Ipilimumab	3mg/kg	Day 1	IV over 90 minutes	Every 21 days ( $\pm 2$ days) for a maximum of 4 cycles

7.3 Patients treated with bevacizumab/*nab*-paclitaxel will always receive the bevacizumab infusion FIRST followed immediately by the infusion of *nab*-paclitaxel. Treatment will continue until disease progression (PD) or toxicity. A cycle is 28 days ( $\pm 2$  days).

Patients treated with ipilimumab will receive the standard 4 infusions (4 cycles) of ipilimumab currently approved by the FDA (or less if toxicity or there is clear evidence of tumor progression). A cycle of ipilimumab is 21 days ( $\pm 2$  days).

7.31 **Arm A:** Patients randomized to Arm A will initially receive bevacizumab plus *nab*-paclitaxel until progression (PD). Bevacizumab will be administered on days 1 and 15 of a 28-day ( $\pm 2$  days) cycle. *Nab*-paclitaxel will be administered on days 1 (following bevacizumab), 8, and 15 (following bevacizumab) of a 28-day cycle ( $\pm 2$  days).

Some patients will be allowed to proceed on to treatment with ipilimumab  $\leq 2$ -4 weeks following disease progression on bevacizumab/*nab*-paclitaxel treatment. Patients will undergo an assessment of ECOG PS, blood chemistries levels, and tumor size (see Section 4.0). *If any one of the following is true*, the patient **may not** continue on to the Ipilimumab phase of the study:

- ECOG performance score (PS):  $\geq 2$
- Tumor fails to meet RECIST criteria for measurable disease
- ANC  $< 1500/\text{mL}$
- PLT  $< 100,000 \times 10^9/\text{L}$
- Hgb  $< 9\text{g/dL}$  (patients may be transfused to meet Hgb requirement)
- Creatinine  $\geq 1.5 \times \text{ULN}$
- Total bilirubin  $\geq 1.5 \text{ mg/dL}$  (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
- SGOT (AST)  $\geq 2.5 \times \text{ULN}$
- Urine dipstick for proteinuria  $\geq 2+$  and a 24 hour urine collection result demonstrating  $> 1\text{g}$  of protein in 24 hours
- $\geq$  grade 2 peripheral sensory or motor neuropathy
- Evidence of brain metastasis on MRI or CT

7.311 **Patients who are eligible and willing to continue on to ipilimumab treatment phase:** Patients who are eligible and willing to continue on to ipilimumab treatment phase must begin ipilimumab treatment  $\leq 2$ -4 weeks after PD. Patients will receive ipilimumab on day 1 of a 21-day cycle ( $\pm 2$  days) for a maximum of 4 cycles (see Section 13.0).

- If PD during ipilimumab treatment, patients will go to Event Monitoring.
- If no PD at the completion of ipilimumab treatment, patients will go to Observation every 8 weeks until PD. At the time of PD, patients will go to Event Monitoring.

7.312 **Patients who are not eligible or choose not to continue on to ipilimumab:** Patients who are not eligible or choose not to continue on to ipilimumab will go to Event Monitoring (see Section 13.0).

7.32 **Arm B:** Patients randomized to Arm B will receive ipilimumab which will be administered on day 1 of each cycle for a maximum of four (4) 21-day ( $\pm 2$  days) cycles. At the completion of ipilimumab treatment, patients will go to Observation every 8 weeks until PD.

At PD, patients will undergo an assessment of ECOG PS, blood chemistries levels, and tumor size (see Section 4.0). *If any one of the following is true*, the patient **may not** continue on to the bevacizumab plus *nab*-paclitaxel phase of the study:

- ECOG performance score (PS):  $\geq 2$
- tumor fails to meet RECIST criteria for measurable disease
- ANC  $< 1500/\text{mL}$
- PLT  $< 100,000 \times 10^9/\text{L}$

- Hgb < 9g/dL (patients may be transfused to meet Hgb requirement)
- Creatinine  $\geq 1.5$  x ULN
- Total bilirubin  $\geq 1.5$  mg/dL (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
- SGOT (AST)  $\geq 2.5$  x ULN
- Urine dipstick for proteinuria  $\geq 2+$  and a 24 hour urine collection result demonstrating > 1g of protein in 24 hours
- $\geq$  grade 2 peripheral sensory or motor neuropathy
- Evidence of brain metastasis on MRI or CT

Additionally patients who undergo the optional research biopsy at time of progression must not initiate therapy with *nab*-paclitaxel and bevacizumab <7 days of biopsy.

7.321 **Patients who are eligible and choose to continue on to the bevacizumab plus *nab*-paclitaxel phase:** Patients who are eligible and choose to proceed to bevacizumab plus *nab*-paclitaxel treatment must begin treatment  $\leq 2-4$  weeks after PD. Patients will receive bevacizumab on days 1 and 15 and *nab*-paclitaxel on days 1 (following bevacizumab), 8, and 15 (following bevacizumab) of a 28-day cycle ( $\pm 2$  days). Treatment will continue until PD. At the time of PD, patients will go to Event Monitoring. (see Section 13.0).

7.322 **Patients who are not eligible or who choose not to continue on bevacizumab plus *nab*-paclitaxel:** Patients who are not eligible or choose not to continue on bevacizumab plus *nab*-paclitaxel will go on to Event Monitoring (see Section 13.0).

- 7.4 For this protocol during active treatment and observation phases, the patient must return to the consenting ACCRU institution for evaluation as specified in the test schedule (See section 4.0).
- 7.5 Treatment by a local medical doctor (LMD) is not allowed.
- 7.6 If there is an interruption of treatment of  $\geq 21$  days due to patient request, scheduling issues, inclement weather, vacation, etc. the patient may not restart treatment and will enter the event monitoring phase of the study.

## 8.0 Dosage Modifications Based on Adverse Events

- 8.1 Dose modifications are based on the adverse events that develop. These modifications should be regarded as guidelines to result in mild-to moderate, but not debilitating side effects. If multiple toxicities are seen, administer dose based on greatest reduction required for any single toxicity observed.
- 8.2 **There are no dose reductions for ipilimumab based on adverse events.** If treatment is held greater than 3 weeks without resolution of adverse events to levels specified in Dose modification tables found in Sections 8.4 - 8.7 then treatment should be discontinued and patients go to Event Monitoring (see Section 13.0)
- 8.3 A maximum of 2 dose reductions for *nab*-paclitaxel are allowed. **There are no dose reductions for bevacizumab based on adverse events.** If a patient requires a 3<sup>rd</sup> dose reduction based on adverse events or treatment is held greater than 4 weeks without resolution of adverse event, then treatment should be discontinued and patients go to Event Monitoring (see Section 13.0).

**ALERT:** ADR reporting may be required for some toxicities (See Section 10.0)

### Dose Levels

Dose Level	Bevacizumab	<i>Nab</i> -paclitaxel
0*	10mg/kg	150mg/m <sup>2</sup>
-1	10 mg/kg	100mg/m <sup>2</sup>
-2	10 mg/kg	75 mg/m <sup>2</sup>

\*Starting dose level

**Use the following definitions to determine actions in the Action columns of the following tables:**

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.4 Dose modifications for *nab-paclitaxel* based on interval toxicity during treatment: **Days 8 & 15**

8.41 If *nab-paclitaxel* is omitted due to an adverse event (days 8 or 15), bevacizumab can be continued if there are no contraindications to its administration (see Table 8.5).

<b>TREATMENT MODIFICATIONS FOR <i>NAB-PACLITAXEL</i> ON CYCLE DAYS 8 &amp; 15</b> Use Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0* unless otherwise specified.		
CTCAE Category	Adverse Event	Dose Reduction
Investigations	Neutrophil count decreased $\geq$ grade 3	<b>Day 8:</b> Omit dose that day and retreat at same dose level on day 15 if counts have recovered to $\leq$ grade 2. <b>Day 15:</b> Omit dose that day. <b>NOTE:</b> If Day 8 and 15 of a cycle are omitted, then subsequent cycles of <i>nab-paclitaxel</i> are to be administered at the next lower dose.
	Platelet count decreased $\geq$ grade 2	<b>Day 8:</b> Omit dose that day and retreat at same dose level on day 15 if counts have recovered to $\leq$ grade 1. <b>Day 15:</b> Omit dose that day. <b>NOTE:</b> If Day 8 and 15 of a cycle are omitted, then subsequent cycles of <i>nab-paclitaxel</i> are to be administered at the next lower dose.
Nervous system disorders	Peripheral sensory neuropathy OR Peripheral motor neuropathy $\geq$ grade 2	Omit dose that day. If resolved to $<$ grade 2 by next scheduled dose, then dose reduce by one level (see below). If treatment needs to be held $>$ 4 weeks, discontinue study treatment and go to Event Monitoring.
All other non-hematologic adverse events	$\geq$ grade 3	Omit dose that day. If resolved to $\leq$ grade 2, then dose reduce by one level. If treatment needs to be held $>$ 4 weeks, discontinue study treatment and go to Event Monitoring.

\*[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

8.5 Dose modifications for *nab-paclitaxel* at time of re-treatment on subsequent cycles: **Day 1.**

8.51 If *nab-paclitaxel* is held on day 1 due to an adverse event, bevacizumab should also be held.

<b>TREATMENT MODIFICATIONS FOR <i>NAB-PACLITAXEL</i> ON SUBSEQUENT CYCLES: DAY 1</b> Use Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 unless otherwise specified.		
CTCAE category	Adverse Event	Dose Reduction
Investigations	Neutrophil count decreased $\geq$ grade 2	Hold <i>nab-paclitaxel</i> until counts < grade 2 then decrease by ONE dose level.  If treatment needs to be held >4 weeks, discontinue study treatment and go to Event Monitoring.
	Platelet count decreased $\geq$ grade 2	Hold <i>nab-paclitaxel</i> until counts < grade 2 then decrease by ONE dose level.  If treatment needs to be held >4 weeks, discontinue study treatment and go to Event Monitoring.
	Aspartate aminotransferase increased or Alkaline phosphatase increased $\geq$ grade 2	Hold <i>nab-paclitaxel</i> until resolved to < grade 2 then dose reduce by ONE dose level.  If treatment needs to be held >4 weeks, discontinue study treatment and go to Event Monitoring. .
Nervous system Disorders	Peripheral sensory neuropathy $\geq$ grade 2	Hold <i>nab-paclitaxel</i> until resolved to < grade 2 then reduce dose by ONE dose level.  If treatment needs to be held >4 weeks, discontinue study treatment and go to Event Monitoring.
All other non-hematologic adverse events	$\geq$ grade 3	Hold <i>nab-paclitaxel</i> until resolved to $\leq$ grade 2 then reduce dose by ONE dose level.  If treatment needs to be held >4 weeks, discontinue study treatment and go to Event Monitoring.

8.6 Dose modifications for **bevacizumab** treatment: **Days 1 and 15**

8.61 **Dose reductions for bevacizumab are not allowed.** The scheduled treatment is either given at full dose or held/omitted.

8.62 If bevacizumab is temporarily held (**days 1 and 15**), treatment with *nab-paclitaxel* can continue if there are no contraindications to administration. If bevacizumab has to be held for >4 weeks, discontinue all treatment and go to Event Monitoring (see Section 13.3).

**Use Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 unless otherwise specified.**

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	TREATMENT MODIFICATION
Investigations	Neutrophil count decreased $\geq$ grade 3	<p><b>Day 1:</b> Hold until neutrophil count &lt;grade 3.</p> <p><b>Day 15:</b> Omit dose.</p> <p>If treatment needs to be held &gt;4 weeks, discontinue study treatment and go to Event Monitoring.</p>
	Platelet count decreased $\geq$ grade 2	<p><b>Day 1:</b> Hold until platelet count &lt;grade 2.</p> <p><b>Day 15:</b> Omit dose.</p> <p>If treatment needs to be held &gt;4 weeks, discontinue study treatment and go to Event Monitoring.</p>
Gastrointestinal disorders	Colonic perforation Any grade	Discontinue all study treatment and proceed to Event Monitoring
	Colonic obstruction  grade 1  grade 2	<p>Continue patient on study for partial bowel obstruction NOT requiring medical intervention.</p> <p>Omit bevacizumab for partial obstruction requiring medical intervention. If resolved to grade 0 within 4 weeks, resume treatment. If treatment needs to be held &gt;4 weeks, discontinue all study treatment and go to Event Monitoring.</p>
	grade 3 or 4	For complete bowel obstruction, discontinue study treatment and proceed to Event Monitoring.

**Continued on next page**

<b>CTCAE System/Organ/Class (SOC)</b>	<b>ADVERSE EVENT</b>	<b>TREATMENT MODIFICATION</b>
Cardiac disorders	Acute coronary syndrome  Any grade	Discontinue study treatment and proceed to Event Monitoring.
	Left ventricular systolic dysfunction grade 3  grade 4	Omit until resolution to grade $\leq 1$ . If treatment needs to be held >4 weeks, discontinue all study treatment and go to Event Monitoring .  Discontinue study treatment and proceed to Event Monitoring.
	Myocardial infarction  Any grade	Discontinue treatment and proceed to Event Monitoring.
	Cardiac disorders-other: Angina  Any grade	Discontinue treatment and proceed to Event Monitoring.
Nervous system disorders	Reversible posterior leukoencephalopathy syndrome  OR  Intracranial hemorrhage  $\geq$ grade 2	Discontinue study treatment and proceed to Event Monitoring.
	Ischemia cerebrovascular  Any grade	Discontinue treatment and proceed to Event Monitoring.
	Transient ischemic attack  Any grade	Discontinue treatment and proceed to Event Monitoring.
Respiratory, thoracic and mediastinal disorders	Bronchopulmonary hemorrhage  $\geq$ grade 2	Discontinue study treatment and proceed to Event Monitoring.

Vascular disorders	Thromboembolic event  grade 3 or asymptomatic grade 4	<ul style="list-style-type: none"> <li>• Omit bevacizumab treatment. If the planned duration of full-dose anticoagulation is &lt;2weeks, bevacizumab should be held until the full-dose anticoagulation period is over.</li> <li>• If the planned duration of full-dose anticoagulation is &gt;2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation <b>IF</b> <u>all</u> of the criteria below are met:                         <ul style="list-style-type: none"> <li>– The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or on stable dose of heparin prior to resuming bevacizumab treatment.</li> <li>– The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions)</li> <li>– The subject must not have had hemorrhagic events while on study</li> </ul> </li> <li>• If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.</li> </ul>
	Symptomatic grade 4	Discontinue treatment and proceed to Event Monitoring.
	Hypertension Hypertension should be treated as per general practice. If hypertension (i.e., systolic blood pressure $\geq 150$ mmHg and/or diastolic blood pressure $\geq 100$ mmHg) persists despite treatment, hold treatment until blood pressure is below this level.	If treatment needs to be held >4 weeks due to uncontrolled hypertension, discontinue study treatment and go to Event Monitoring.
	Vascular disorders-other: Any arterial thromboembolic event  Any grade	Discontinue treatment and proceed to Event Monitoring.

<p>Renal and urinary disorders</p>	<p>Proteinuria</p> <p>grade 3 (urine collection &gt;3.5 g/24 hour or dipstick 4+)</p> <p>grade 4 (nephritic syndrome)</p>	<p>Omit bevacizumab until <math>\leq</math> grade 2, as determined by 24 hr. collection <math>\leq</math>3.5 g. If treatment needs to be held <math>\geq</math>4 weeks, discontinue treatment and proceed to Event Monitoring.</p> <p>Discontinue treatment and proceed to Event Monitoring.</p>
<p>Injury, poisoning and procedural complications</p>	<p>Wound dehiscence (requiring medical or surgical intervention)</p>	<p>Discontinue treatment and proceed to Event Monitoring.</p>
<p>Immune system disorders</p>	<p>Allergic reaction (hypersensitivity)</p> <p>grade 3 or 4</p>	<p>Discontinue study treatment and proceed to Event Monitoring.</p>
<p>Respiratory thoracic and mediastinal disorders</p>	<p>Adult Respiratory Distress Syndrome (ARDS)</p> <p>Any grade</p>	<p>Discontinue study treatment and proceed to Event Monitoring.</p>
	<p>Bronchospasm</p> <p>Any grade</p>	<p>Discontinue study treatment and proceed to Event Monitoring.</p>
<p>Other clinically significant AEs at least possibly attributable to bevacizumab (except controlled nausea/vomiting and any Gr 3+ hemorrhage)</p>	<p>grade 3</p> <p>grade 4</p>	<p>Omit treatment until toxicities return to baseline or <math>\leq</math> grade 1, then retreat based on interval toxicities. If treatment needs to be held &gt;4 weeks, discontinue study treatment and proceed to Event Monitoring.</p> <p>Discontinue study treatment and proceed to Event Monitoring.</p> <p>Grade 3-4 hemorrhage, discontinue treatment and proceed to Event Monitoring.</p>

8.7 Dose modifications for **ipilimumab on day 1 of each treatment dose**

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	TREATMENT MODIFICATION
Gastrointestinal disorders	<p>Diarrhea</p> <p>Grade 2 <b>AND</b> symptoms <math>\leq</math>1 week</p> <p>Grade 2 <b>AND</b> symptoms &gt; 1 week</p> <p><math>\geq</math>grade 3</p>	<p>See Section 9.9b1 for treatment of diarrhea.</p> <p>Hold ipilimumab until symptoms resolved to <math>\leq</math> grade 1. If treatment needs to be held &gt;3 weeks, discontinue study treatment and go to Event Monitoring.</p> <p>Initiate steroid therapy and hold ipilimumab until symptoms resolved to <math>\leq</math> grade 1. If treatment needs to be held &gt;3 weeks, discontinue study treatment and go to Event Monitoring.</p> <p>Discontinue study treatment and go to Event Monitoring.</p>
	Colonic perforation Any Grade	Discontinue study treatment and go to Event Monitoring.
Endocrine disorders	<p>Hypothyroidism</p> <p>grade 2</p> <p><math>\geq</math>grade 3</p>	<p>Hold ipilimumab until resolved to <math>\leq</math>grade 1 and initiate thyroid replacement therapy. If treatment needs to be held &gt;3 weeks, discontinue study treatment and go to Event Monitoring.</p> <p>Discontinue study treatment and go to Event Monitoring. Initiate thyroid replacement and steroid therapy per 9.0</p>

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	TREATMENT MODIFICATION
Nervous system disorders	<p>Any Nervous System Disorders</p> <p>grade 2</p> <p>≥grade 3</p>	<p>Hold ipilimumab until resolved to ≤grade 1 and initiate steroid therapy. If treatment needs to be held &gt;3 weeks, discontinue study treatment and go to Event Monitoring..</p> <p>Discontinue study treatment and go to Event Monitoring. . Initiate steroid therapy per 9.0.</p>
Skin and subcutaneous tissue disorders	<p>Rash maculo-papular</p> <p>Grade 1 symptomatic <b>OR</b> Grade 2</p> <p>≥ Grade 3</p>	<p>Hold ipilimumab until symptoms resolved to ≤grade 1 <b>AND</b> asymptomatic. Initiate therapy with topical steroids (grade 1 symptomatic) and/or systemic steroids (grade 2). If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue study treatment and go to Event Monitoring. Initiate therapy with systemic steroids +/- topical steroids per 9.0</p>
Investigations	<p>Aspartate aminotransferase increased or Alanine aminotransferase increased</p> <p>grade 2</p> <p>≥ grade 3</p>	<p>Hold ipilimumab and initiate steroids until levels are ≤3 x ULN (grade 1). Monitor twice weekly until resolved to ≤grade1. If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue ipilimumab and go to Event Monitoring. Initiate therapy with steroids per 9.0 and monitor twice weekly until resolved to ≤grade1.</p>

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	TREATMENT MODIFICATION
	<p>Blood bilirubin increased</p> <p>grade 2</p> <p>≥grade 3</p>	<p>Hold ipilimumab and monitor twice weekly until levels are ≤grade1. Initiate therapy with steroids per 9.0. If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue ipilimumab and go to Event Monitoring. Initiate therapy with steroids per 9.0 and monitor twice weekly until resolved to ≤grade 1.</p>
Immune systems disorders	<p>Any Immune systems disorders</p> <p>Grade 2</p> <p>≥ Grade 3</p>	<p>Hold ipilimumab and monitor twice weekly until levels are ≤grade1. Initiate therapy with steroids per 9.0. If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue ipilimumab and go to Event Monitoring. Initiate therapy with steroids per 9.0 and monitor twice weekly until resolved to ≤grade1.</p>
Respiratory, thoracic and mediastinal disorders	<p>Pneumonitis</p> <p>grade 2</p> <p>≥grade 3</p>	<p>Hold ipilimumab and monitor twice weekly until levels are ≤grade1. Initiate therapy with steroids per 9.0. If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue ipilimumab and go to Event Monitoring. Initiate therapy with steroids per 9.0 and monitor twice weekly until resolved to ≤grade 1.</p>

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	TREATMENT MODIFICATION
General disorders and administration site conditions	<p>Any General disorders and administration site conditions</p> <p style="text-align: center;">grade2</p> <p style="text-align: center;">≥grade 3</p>	<p>Hold ipilimumab until resolved to ≤grade 1. If treatment needs to be held &gt;3 weeks, discontinue treatment and go to Event Monitoring.</p> <p>Discontinue study treatment and go to Event Monitoring.</p>

## 9.0 Ancillary Treatment/Supportive Care

- 9.1 Hypersensitivity reactions: Patients do not require premedication prior to *nab*-paclitaxel or ipilimumab administration, as hypersensitivity reactions are not expected. In the unlikely event of a hypersensitivity reaction, treatment with antihistamines, H2 blockers, and corticosteroids is recommended. Patients should be pre-medicated with the typical regimen for *nab*-paclitaxel regimens for subsequent cycles. In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent-based *nab*-paclitaxel.
- 9.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record and on the treatment form.
- 9.3 Use of growth factors prophylactically during this trial is discouraged. Oncologists are urged to follow the ASCO guidelines ([www.asco.org](http://www.asco.org)) and to discontinue growth factors 24 hours prior to initiation of the next cycle of chemotherapy. The use of any growth factor must be documented in the patients' record and on the treatment form.
- 9.4 Patients may not enroll in a different clinical study, including Cancer Control studies, in which investigational procedures or agents are being used, while participating in this study.
- 9.5 Patients must terminate study treatment if they are to receive radiation therapy for palliative reasons as it impacts upon assessing response.
- 9.6 Patients should be pre-medicated according to institutional policy with antiemetics for patients receiving taxane/platinum therapy.
- 9.7 General patient monitoring and supportive care guidelines

- 9.71 Patients should be carefully monitored during the treatment phase and then followed appropriately. Prior to each bevacizumab infusion, patients should be carefully assessed, with special attention to blood pressure, proteinuria, bleeding events as well as other adverse events. Decisions for retreatment or dose modifications/interruption should follow the guidelines in Sections 8.4
- 9.72 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 treating physician or his/her designee every 2 weeks until the event is resolved or determined to be irreversible.
- 9.721 Hypertension  
Blood pressure should be assessed at least weekly during the first cycle and before each administration of bevacizumab (days 1 and 15) thereafter. High blood pressure may require initiation or increase in antihypertensive medication according to routine clinical practice. Bevacizumab treatment modifications should follow the instructions in Section 8.4.
- 9.8 If patients on treatment with bevacizumab require elective major surgery, bevacizumab should be discontinued for at least 4-8 weeks prior to the surgical procedure.
- 9.9a Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 4.0 Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment. The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above (and Section 8.0). When the subject's symptoms have completely resolved, the 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.
- 9.9b Side effect management for Ipilimumab toxicities- these are to be regarded as guidelines for managing toxicity that occurs with ipilimumab therapy and should not replace clinical judgement (i.e - patients with grade 1 rash may require systemic steroids).
- 9.9b1 Diarrhea (see Section 8.7)
- 9.9b11 Grade 1- without abdominal pain/or blood in stool and symptoms, manage symptomatically. Infectious etiologies should be ruled out. May continue ipilimumab. Instruct patients to report any increase in stools.
- 9.9b12 Grade 2- without abdominal pain/or blood in stool and symptoms < **1 week**, and resolve to grade 0 or 1- continue to monitor. Infectious etiologies should be ruled out. Hold ipilimumab until symptoms resolved to  $\leq$  Grade 1.

9.9b13 Grade 2- symptoms **>1 week**, should be started on systemic steroid therapy (0.5 mg/kg/day prednisone or equivalent- can be given in two doses- especially for patients that have nocturnal diarrhea).\*\* Infectious etiologies should be ruled out. Hold ipilimumab until symptoms resolved to  $\leq$  Grade 1.

9.9b14 Grade 3 or greater- **who have other etiologies ruled out** should be started on systemic steroids at 1-2 mg/kg/day prednisone or equivalent (may be given in two daily doses-especially for patients that have nocturnal diarrhea).\*\* Assess for dehydration. Patients may require hospitalization for IV steroids (1-2 mg/kg/day methylprednisolone) Discontinue ipilimumab. Patients without improvement in symptoms over 3-5 days, consider the following: endoscopy, budesonide 12 mg orally once daily, steroid enemas, or GI consultation.

\*\* Once patients have improvement of symptoms to grade 0 or 1 taper of steroids should occur over at least 1 month- if patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone **FIRST**(over 2 to 3 weeks) before tapering of budesonide.

**Do NOT administer loperamide in patients with  $\geq$  Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.**

**If at any time patients experience diarrhea with the following symptoms: fever or abdominal pain patients should have a CT scan of the abdomen to rule out perforation. Emergent surgical evaluation should be performed if perforation is found.. If a patient has bloody diarrhea, a Gastroenterology consult should be obtained. A Gastroenterology consult should be obtained if provider is considering infliximab for treatment of colitis.**

**For all patients- assess hydration status and monitor electrolytes, including magnesium.**

9.9b2 Rash (see Section 8.7)

9.9b21 Grade 1 symptomatic or any Grade 2- Hold ipilimumab until resolved  $\leq$  Grade 1 and ASYMTOMATIC. Initiate therapy with topical (Grade 1 symptomatic) or systemic steroids (Grade 2).

9.9b22 Grade 3 or greater- discontinue ipilimumab. Initiate systemic steroid therapy.

9.9b3 Hypothyroidism (see Section 8.7)

9.9b31 Grade 2- Initiate thyroid replacement. Hold ipilimumab until resolved to  $\leq$  Grade 1

- 9.9b32 Grade 3 or greater- Discontinue ipilimumab. Initiate thyroid replacement therapy. Initiate systemic steroid therapy
- 9.9b4 Neurological
- 9.9b41 **Mild** symptoms (grade 1) – Rule out other causes (i.e CNS metastasis) and continue ipilimumab and monitor patient for any worsening.
- 9.9b42 **Moderate** symptoms (grade 2). Rule out other causes (i.e CNS metastasis). Treat symptomatically. Hold ipilimumab until symptoms resolved to grade 0 or 1. Consider starting low dose steroids (i.e 0.5 mg/kg/day).
- 9.9b43 **Severe** symptoms (grade 3 or 4).
- a. Grade 3-4 **sensory**- Rule out other causes (i.e CNS metastasis)
    - i. Treat with high dose steroids (1-2 mg/kg/day). Consider IV steroids.
    - ii. Refer to Neurology.
    - iii. Once symptoms resolve to  $\leq$  grade 2 can start steroid taper\*
  - b. Grade 3-4 **motor**\*\* - Rule out other causes (i.e CNS metastasis).
    - i. Treat with high dose steroids (1-2 mg/kg/day). Consider IV steroids.
    - ii. Refer to Neurology.
    - iii. Once symptoms resolve to  $\leq$  grade 2 can start steroid taper\*
- 9.9b5 Liver dysfunction (AST or ALT)
- 9.9b51 AST or ALT  $\leq$  2.5 ULN- No change in treatment
- 9.9b52 AST or ALT  $>$ 2.5 -3 ULN or Grade 2- Hold ipilimumab until levels are  $\leq$  2.5 ULN. Monitor levels twice weekly until resolved. Consider initiating systemic steroids.
- 9.9b53 AST or ALT  $\geq$  Grade 3- Discontinue ipilimumab. Initiate systemic steroid therapy.
- 9.9b6 Liver dysfunction (Total Bilirubin)
- 9.9b61 Grade 1- No change in treatment
- 9.9b62 Grade 2- Hold ipilimumab and monitor levels until resolved to  $\leq$  Grade 1. Consider initiating systemic steroids.
- 9.9b63 Grade 3 or greater- Discontinue ipilimumab. Monitor levels until resolved to  $\leq$  Grade 1. Initiate therapy with steroids.
- 9.9b7 Pneumonitis
- 9.9b71 Grade 1- No change in treatment

- 9.9b72 Grade 2- Hold ipilimumab until resolved to  $\leq$  Grade 1 and initiate steroids
- 9.9b73 Grade 3 or greater- Discontinue ipilimumab, consider hospitalization, and initiate systemic steroids
- 9.9b8 General management of other immune related adverse events (not specified above).
- 9.9b81 Grade 1- Observe, rule out other causes, and treat symptomatically
- 9.9b82 Grade 2- Hold Ipilimumab until symptoms resolved to  $\leq$  grade 1, initiate therapy with systemic steroids
- 9.9b83 Grade 3 or higher –Discontinue ipilimumab permanently. Initiate therapy with systemic steroids.
- 9.9b9 Steroid dosing guidelines
  - 9.9b91 Grade 2- Steroids should be initiate at 0.5-1mg/kg/day of prednisone or equivalent.
  - 9.9b92 Grade 3 or greater- Steroids should be initiated at 1-2 mg/kg/day of prednisone or equivalent.

## 10.0 Adverse Event (AE) Reporting and Monitoring

### 10.1 Adverse Event Characteristics

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

- 10.11 Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. First, identify and Grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

#### 10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

**NOTE:** “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

#### 10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

**Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.**

#### 10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

##### **Routine Reporting**

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.52.

**NOTE:** When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

**Expedited Reporting**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.32 **Special Situations for Expedited Reporting**

10.321 **Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events**

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditiously reported.
Blood and lymphatic system disorders	Anemia	≤Grade 3
	Febrile neutropenia	≤Grade 3
Cardiac disorders	Myocardial infarction	≤Grade 3
Gastrointestinal disorders	Nausea	≤Grade 3
	Vomiting	≤Grade 3
	Gastric hemorrhage	≤Grade 3
	Abdominal pain	≤Grade 3
	Diarrhea	≤Grade 3
General disorders and administration site conditions	Fatigue	≤Grade 3
	Fever	≤Grade 3
Immune system disorders	Allergic reaction/ anaphylaxis	≤Grade 3
Injury, poisoning, and procedural complications	Wound dehiscence	≤Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 3
	White blood cell decreased	≤Grade 4
	AST	≤Grade 3
	Alkaline Phosphatase	≤Grade 3
	Total Bilirubin	≤Grade 3
Musculoskeletal and connective tissue disorders	Arthralgia	≤Grade 3
	Myalgia	≤Grade 3
Nervous system disorders	Intracranial hemorrhage	≤Grade 3
	Leukoencephalopathy	≤Grade 3
	Peripheral sensory neuropathy	≤Grade 3
Renal and urinary disorders	Proteinuria	≤Grade 4
Respiratory, thoracic and mediastinal disorders	Bronchopulmonary hemorrhage	≤Grade 3
Skin and subcutaneous tissue disorders	Rash maculo-papular	≤Grade 4
Vascular disorders	Hypertension	≤Grade 3
	Thromboembolic event	≤Grade 3

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event (regardless of hospitalization).

10.322 **Persistent or Significant Disabilities/Incapacities**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported

immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

#### 10.323 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Reportable categories of Death
- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

#### 10.324 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.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.325 Second Malignancy

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

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

<p><b>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</b>  <b>NOTE:</b> Investigators <b>MUST</b> immediately report to the sponsor <b>ANY</b> Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)                  An adverse event is considered serious if it results in <b>ANY</b> of the following outcomes:</p> <ol style="list-style-type: none"> <li>1) Death</li> <li>2) A life-threatening adverse event</li> <li>3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours</li> <li>4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions</li> <li>5) A congenital anomaly/birth defect.</li> <li>6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).</li> </ol>				
<p><b>ALL SERIOUS</b> adverse events that meet the above criteria <b>MUST</b> be immediately reported to the sponsor within the timeframes detailed in the table below.</p>				
<b>Hospitalization</b>	<b>Grade 1 Timeframes</b>	<b>Grade 2 Timeframes</b>	<b>Grade 3 Timeframes</b>	<b>Grade 4 &amp; 5 Timeframes</b>
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	
<p><b>NOTE:</b> Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.321.  <u><b>Expedited AE reporting timelines are defined as:</b></u></p> <ul style="list-style-type: none"> <li>○ “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.</li> <li>○ “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.</li> </ul>				
<p><sup>1</sup>Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:  <b>Expedited 24-hour notification followed by complete report within 3 calendar days for:</b></p> <ul style="list-style-type: none"> <li>• All Grade 4, and Grade 5 AEs</li> </ul> <p><b>Expedited 7 calendar day reports for:</b></p> <ul style="list-style-type: none"> <li>• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization</li> <li>• Grade 3 adverse events</li> </ul> <p><sup>2</sup> For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.                  Effective Date: May 5, 2011</p>				

**Additional Instructions:**

1. Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via expedited mechanisms if the event occurs following treatment on a trial under an IND.

2. Use the ACCRU protocol number and the protocol-specific patient ID provided during trial registration/randomization on all reports.

The above expedited reports (24-hour and 3- or 7-day) must be submitted via the [REDACTED]. Submit reports to the ACCRU SAE Coordinator via fax [REDACTED].

3. **Mayo Clinic Cancer Center (MCCC) Institutions: Fax a copy of the report to both Celgene and Genentech using the fax numbers provided below.** Provide copies, along with the UPIRTSO cover sheet, by fax ([REDACTED]) to the MCCC Regulatory Affairs Unit (RAU) Regulatory Affairs Specialist who will determine and complete IRB reporting. The RAU will submit to the ACCRU SAE Coordinator and the ACCRU IND Coordinator to determine if FDA submission is needed.
4. **Non-Mayo ACCRU Sites:** Submit reports to the ACCRU SAE Coordinator via fax [REDACTED]. Once the ACCRU SAE Coordinator receives the report via fax, the ACCRU SAE Coordinator will forward a copy of the above expedited reports to:

- **The ACCRU IND Coordinator** who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
- **Celgene:** Expedited Reporting by Investigator to Celgene:  
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-MEL-ACCRU-0090) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.



- **Genentech:** Genentech will be informed in writing of any SAE within 24 hours/1 business day of receipt of the fax. The fax will be sent to Genentech Drug Safety at:



- **Pregnancy** – If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the bevacizumab should be reported as an SAE.

## 10.5 Other Required Reporting

- 10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class	Adverse/Event Symptoms	Baseline	Each Evaluation
Blood and lymphatic system disorders	Anemia	X	X
	Febrile neutropenia		X
Cardiac disorders	Myocardial infarction		X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
	Abdominal pain	X	X
	Baseline # stools	X	
	Diarrhea		X
General disorders and administration site conditions	Fatigue	X	X
	Fever		X
Immune system disorders	Allergic reaction		X
	Anaphylaxis		X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White blood cell decreased	X	X
	Aspartate aminotransferase increased	X	X
	Alkaline phosphatase increased	X	X
	Blood bilirubin increased	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
	Myalgia	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X

- 10.511 **Genentech AEs of Special Interest (AESI):** AEs of Special Interest for Avastin are defined by Genentech as a potential safety problem identified as a result of ongoing safety monitoring of their product. As such, **surveillance for the AESIs in Appendix III MUST be undertaken at each treatment evaluation. Development of one of these AESIs (grade 1 or severer unless otherwise noted) MUST be reported on the AE case report forms in terms of CTCAE v4.0 grade and attribution.**
- 10.512 **Reconciliation:** The Sponsor (ACCRU) agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format but agree at a minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor (ACCRU) and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.
- 10.513 **Study Close-out:** Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study.
- Avastin Protocols**  
 Email: [REDACTED]  
 Fax: [REDACTED]
- 10.52 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:
- 10.521 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure
- 10.523 Grade 5 AEs (Deaths)
- 10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- 10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

- 10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation Using RECIST Criteria

11.1 Schedule of Evaluations are specified in Section 4.0

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as  $\geq 2.0$  cm with chest x-ray, or as  $\geq 1.0$  cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A malignant lymph node is considered measurable if its short axis is  $\geq 1.5$  cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

**NOTE:** *Tumor lesions in a previously irradiated area are not considered measurable disease.*

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis  $\geq 1.0$  to  $< 1.5$  cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

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

Lymph nodes that have a short axis  $< 1.0$  cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-

up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

#### 11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- 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 scans are preferable.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
    - iii. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

### 11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained 8 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks (see Section 11.44).
- 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.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

## 11.4 Measurement of Effect

### 11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

**Note:** If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph

nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

#### 11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

#### 11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

**Note:** Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

#### 11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  - a. Disappearance of all target lesions.
  - b. Each target lymph node must have reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to  $\geq 1.0$  cm short axis during follow-up.

- b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  - c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the MSD.

#### 11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  - a. Disappearance of all non-target lesions.
  - b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- Progression (PD): At least one of the following must be true:
  - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to  $\geq 1.0$  cm short axis during follow-up.
  - b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  - c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient’s status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

<b>Target Lesions &amp; Target Lymph Nodes</b>	<b>Non-Target Lesions &amp; Non-Target Lymph Nodes</b>	<b>New Sites of Disease</b>	<b>Overall Objective Status</b>
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

\*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to “symptomatic deterioration” if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

- 11.5 All images will be submitted for research purposes. Images should be submitted on CD  $\leq 2$  weeks after collection at the time of progression or death.

Submitted images should be accompanied by a radiology report. Images should represent the entire radiologic assessment for the tumor assessment visit. ACCRU Patient ID number must be on the images and on the radiology report.  
See Appendix II for imaging guidelines and Appendix III for image submission process.

## 12.0 Descriptive Factors

- 12.1 Previous chemotherapy in the metastatic setting: Yes vs. no.
- 12.2 Previous immunotherapy in the metastatic setting: Yes vs. no.
- 12.3 Prior lines of therapy in the metastatic setting: 0 vs. 1 vs. 2.

## 13.0 Treatment/Follow-up Decision at Evaluation of Patient

### 13.1 Arm A patients

- 13.11 Patients receiving bevacizumab/*nab*-paclitaxel treatment who have not had disease progression and have experienced acceptable toxicity will be eligible to continue on bevacizumab/*nab*-paclitaxel until disease progression, unacceptable toxicity or refusal.
- 13.12 Patients who discontinue bevacizumab/*nab*-paclitaxel treatment for reasons other than progression will go to Event Monitoring phase of the trial until death or a maximum of 5 years post-randomization.
- 13.13 Patients who progress during bevacizumab/*nab*-paclitaxel treatment phase will undergo an assessment of ECOG PS, blood chemistries levels, and tumor size (see Section 4.0). If *any one of the following is true*, the patient **may not** continue on to Ipilimumab treatment phase of the study:
- ECOG performance score (PS):  $\geq 2$
  - tumor fails to meet RECIST criteria for measurable disease
  - ANC  $< 1500/\text{mL}$
  - PLT  $< 100,000 \times 10^9/\text{L}$
  - Hgb  $< 9\text{g}/\text{dL}$  (patients may be transfused to meet Hgb requirement)
  - Creatinine  $\geq 1.5 \times \text{ULN}$
  - Total bilirubin  $\geq 1.5 \text{mg}/\text{dL}$  (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
  - SGOT (AST)  $\geq 2.5 \times \text{ULN}$
  - Urine dipstick for proteinuria  $\geq 2+$  and a 24 hour urine collection result demonstrating  $> 1\text{g}$  of protein in 24 hours
  - $\geq$  grade 2 peripheral sensory or motor neuropathy
  - Evidence of brain metastasis on MRI or CT

- 13.131 Patients who are not eligible to continue on to ipilimumab phase or who choose not to continue on to the ipilimumab phase will go to Event Monitoring phase until death or a maximum of 5 years post-randomization.
- 13.132 Patients who proceed to ipilimumab phase may receive a maximum of 4 cycles of treatment and then proceed to Observation until disease progression. Reasons for not completing 4 cycles of ipilimumab or discontinuation of Observation include: disease progression, patient request, intolerability, and concurrent co-morbid conditions.
- Patients who discontinue ipilimumab treatment or Observation for any reason will go to Event Monitoring until death or a maximum of 5 years post-randomization.

## 13.2 Arm B patients

- 13.21 Patients on ipilimumab treatment who have not had disease progression (PD) and who have experienced acceptable toxicity will be eligible to continue on ipilimumab for a maximum of 4 cycles of treatment.
- 13.211 Patients who discontinue ipilimumab treatment for reasons other than progression will go to Event Monitoring phase until death or a maximum of 5 years post-randomization.
- 13.212 Patients who progress during ipilimumab treatment will undergo an assessment of ECOG PS, blood chemistries levels, and tumor size (see Section 4.0). If *any one of the following is true*, the patient **may not** continue on to the bevacizumab/*nab*-paclitaxel phase of the study:
- ECOG performance score (PS):  $\geq 2$
  - tumor fails to meet RECIST criteria for measurable disease
  - ANC  $< 1500/\text{mL}$
  - PLT  $< 100,000 \times 10^9/\text{L}$
  - Hgb  $< 9\text{g}/\text{dL}$  (patients may be transfused to meet Hgb requirement)
  - Creatinine  $\geq 1.5 \times \text{ULN}$
  - Total bilirubin  $\geq 1.5 \text{mg}/\text{dL}$  (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
  - SGOT (AST)  $\geq 2.5 \times \text{ULN}$
  - Urine dipstick for proteinuria  $\geq 2+$  and a 24 hour urine collection result demonstrating  $> 1\text{g}$  of protein in 24 hours
  - $\geq$  grade 2 peripheral sensory or motor neuropathy
  - Evidence of brain metastasis on MRI or CT

- 13.2121 Patients who are not eligible or choose not to proceed to bevacizumab/*nab*-paclitaxel treatment phase will go to Event Monitoring phase until death or a maximum of 5 years post-randomization.
- 13.2122 Patients who are eligible and choose to proceed to bevacizumab/*nab*-paclitaxel treatment phase will continue treatment until PD, unacceptable toxicity, or refusal and then go to Event Monitoring phase until death or a maximum of 5 years post-randomization.
- 13.213 Patients who complete 4 cycles of ipilimumab treatment without disease progression will enter the Observation phase of the study until PD is reported.
- 13.2131 Patients who progress during observation phase will undergo an assessment of ECOG PS, blood chemistries levels, and tumor size (see Section 4.0). *If any one of the following is true*, the patient **may not** continue on to the bevacizumab/*nab*-paclitaxel phase of the study:
- ECOG performance score (PS):  $\geq 2$
  - tumor fails to meet RECIST criteria for measurable disease
  - ANC  $< 1500/\text{mL}$
  - PLT  $< 100,000 \times 10^9/\text{L}$
  - Hgb  $< 9\text{g/dL}$  (patients may be transfused to meet Hgb requirement)
  - Creatinine  $\geq 1.5 \times \text{ULN}$
  - Total bilirubin  $\geq 1.5 \text{ mg/dL}$  (exception: patients with documented Gilbert's syndrome are allowed to participate despite elevated bilirubin)
  - SGOT (AST)  $\geq 2.5 \times \text{ULN}$
  - Urine dipstick for proteinuria  $\geq 2+$  and a 24 hour urine collection result demonstrating  $> 1\text{g}$  of protein in 24 hours
  - $\geq$  grade 2 peripheral sensory or motor neuropathy
  - Evidence of brain metastasis on MRI or CT
- 13.2132 Patients who are not eligible or choose not to proceed to bevacizumab/*nab*-paclitaxel treatment phase will go to the Event Monitoring phase until death or a maximum of 5 years post-randomization.
- 13.2133 Patients who are eligible and choose to proceed to bevacizumab/*nab*-paclitaxel treatment phase will continue treatment until PD, unacceptable toxicity, or refusal and then go to Event Monitoring phase until death or a maximum of 5 years post-randomization.

13.3 Arm A and Arm B

- 13.31 Patients who wish to receive non-protocol, anti-cancer therapy will discontinue all study treatment and enter the Event Monitoring phase. Once a patient has entered the Event Monitoring phase of the trial, his/her therapy is at the discretion of the treating physician.
- 13.32 If an eligible patient refuses to begin study treatment following registration/randomization (and is classified as a cancel by the ACCRU Research Base), all on-study materials must be submitted to the Research Base.
- 13.33 A patient is deemed *ineligible* if at the time of registration/randomization, the patient did not satisfy each and every eligibility criteria for study entry.
  - If the patient never received any study treatment, on-study materials (with the exception of biospecimens) must be submitted. No further follow-up is required.
  - If the patient is receiving study treatment at the time the ineligibility is discovered, the patient may continue on study at the discretion of the treating physician as long as there are no safety concerns, and the patient was properly registered. All protocol procedures must be followed. Otherwise, the patient enters the Event Monitoring phase of the study.

**14.0 Body Fluid Biospecimens**

14.1 Body Fluid Biospecimen Submission

14.11 Summary table of Body Fluid Biospecimens

Type of biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for specimen submission
Blood/blood products (sodium Heparin green top whole blood)	Mandatory for <b>MCR patients ONLY</b>	Prior to first cycle of Ipilimumab and prior to first cycle of BEV/nab-paclitaxel	Analysis of changes in immune homeostasis (Section 14.412)	Section 14.2

14.2 Blood/Blood Products Handling

- 14.21 **Kits are required for this study.** Kits contain supplies and instructions for collecting, processing, and shipping specimens. Kits may be obtained by contacting [REDACTED] in Dr. Markovic’s Hematology/Oncology laboratory.
- 14.22 Kits may be collected Monday through Friday.
- 14.23 Label specimen tubes with protocol number, ACCRU patient ID number, and time and date blood drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Tables of Research Blood/Blood Products to Be Collected for This Protocol

**ARMS A & B SAMPLES Rochester, Minn. Patients Only**

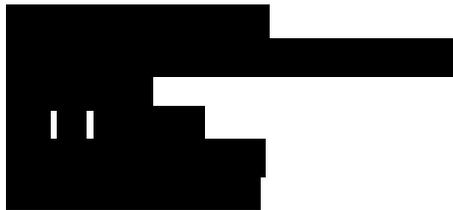
Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed	Prior to day 1 Ipilimumab	Prior to day 1 of BEV/nab-paclitaxel	Process at site?	Storage/shipping conditions <sup>1</sup>
Mandatory	Heparin (dark green)	10 mL (5)	Whole Blood	X	X	No	Ambient

<sup>1</sup> After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

14.251 Verify ALL sections of the ACCRU Blood Specimen Submission Form, protocol Blood Requisition Form, and specimen collection labels are completed and filled in correctly. Enter information from the ACCRU Blood Specimen Submission Form into the remote data entry system ≤7 days after specimen collection (see Forms Packet).

14.252 Send heparin tubes ambient or at room temperature to:



14.253 Notify Michael Thompson at the Research Base by phone [redacted] that blood has been shipped.

14.3 Other Body Fluids Handling (None)

#### 14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research:

- 14.411 Angiogenesis – concentrations of multiple soluble mediators of angiogenesis recovered for patient plasma

Specimens will be stored at – 70°C until the time of assay. Plasma samples will be sent to the laboratory of [REDACTED] at [REDACTED] and processed there. Plasma levels of angiogenesis mediators: angiopoietin-2, BMP-9, EGF, endoglin, endothelin-1, FGF-1, FGF-2, follistatin, G-CSF, HB-EGF, HGF, IL-8, leptin, PLGF, VEGF-A, VEGF-C, and VEGF-D (EMD Millipore, Billerica, MA) will be determined

- 14.412 Analysis of changes in immune homeostasis. The studies described below will all be performed in the laboratory of [REDACTED].

- 14.4121 Immunophenotyping of peripheral blood samples. Samples of peripheral blood (pre-treatment for all cycles) will be analyzed for numbers and activation status of T, B, NK and dendritic cells. Peripheral blood lymphocytes will be collected and frozen for batch analysis. Samples will be analyzed for the following: CD3, CD4, CD8, CD20, CD69, CD4/25, CD8/25, CD16/56, CD80, CD86, HLA-DR.

Blood collected through the port is allowable.

- 14.4122 Frequency of cytotoxic T lymphocytes (CTL) specific for recall as well as tumor associated antigens (HLA-A2 patients only).

- 14.41221 Tetramer assay  
Class I tetramers are comprised of monomeric class I heavy chains that have been folded with  $\beta$ 2-microglobulin ( $\beta$ 2M) and specific immunogenic peptides (EBV, CMV, tyrosinase, gp100, MART-1, Beckman/Coulter); these monomers are then biotinylated at sites on their carboxy ends for conjugation into tetramers with PE-avidin. Such tetramers have increased valency and can be mixed with FITC-labeled anti-CD8 antibody to stain peptide-specific CTLs for enumeration by flow cytometry. Single batches of reagents will be used for all analyses. Ongoing quality assurance/quality control (QA/QC) for these assays demonstrate a <15% inter-assay variability for control (standard) samples.

## 15.0 Drug Information

### 15.1 Paclitaxel Protein Bound (Abraxane®, *nab*-paclitaxel)

#### Investigator brochure contact information:

The most current version of the Investigator Brochure will be maintained in the study folder on the ACCRU website. Updated Investigator's Brochures should be obtained from the study folder as they become available.

Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study.

15.11 **Background:** Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is an antineoplastic agent, Antimicrotubular, Taxane derivative. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G<sub>2</sub> mitotic phase, and inhibiting cell replication

15.12 **Formulation:** Paclitaxel protein-bound particles for injectable suspension (albumin-bound) (nanoparticle albumin bound (*nab*) paclitaxel, *nab*-paclitaxel, Abraxane®). *Nab*-paclitaxel is supplied as a white to off-white lyophilized powder containing 100 mg of paclitaxel and approximately 900 mg Albumin Human USP (HA) as a stabilizer in a 50 mL, single-use vial. Each vial of the lyophilized product is reconstituted with 20 mL 0.9% Sodium Chloride Injection, USP to create a suspension of nanoparticles containing 5 mg/mL nanoparticle albumin-bound (*nab*) paclitaxel.

15.13 **Preparation and Storage:** Unreconstituted *nab*-paclitaxel should be stored at controlled room temperature in its carton. Reconstituted *nab*-paclitaxel should be used immediately. If not used immediately, the vial of reconstituted *nab*-paclitaxel must be placed in its carton and be placed in a refrigerator at 2° to 8°C for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes.

**NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of *nab*-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.**

Reconstitute each *nab*-paclitaxel vial by using a 50 or 60 cc sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute (Note: Change the syringes after reconstituting every 3 vials).

- **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
- **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
- Once the injection is complete, allow the vial to sit for a **minimum of 5 minutes** to ensure proper wetting of the lyophilized cake/powder.

- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
- The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use. If using stored, reconstituted *nab*-paclitaxel (within 8 hours, see above), some settling may occur; ensure complete re-suspension by mild agitation prior to use.
- No further dilution is necessary.

Once the exact volume of reconstituted *nab*-paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.

- Inject the calculated dosing volume of reconstituted *nab*-paclitaxel suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. The use of medical devices containing silicone oil as lubricant (i.e. syringes and intravenous bags) to reconstitute and administer *nab*-paclitaxel may result in the formation of proteinaceous strands.
- Visually inspect the reconstituted *nab*-paclitaxel suspension in the intravenous bag prior to administration.
- As with other cytotoxic anticancer drugs, caution should be exercised in handling *nab*-paclitaxel. The use of gloves is recommended. No data currently exist for accidental exposure. However, as with paclitaxel, if *nab*-paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If *nab*-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported for paclitaxel. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (National Institutes of Health, 1983; American Society of Hospital pharmacists, 1990; Occupational Safety and Health Administration, 1996).

**NOTE: Standard PVC IV bags may be used for the infusion.**

- 15.14 **Administration:** Administer the calculated dosing volume of reconstituted *nab*-paclitaxel suspension by IV infusion over 30 minutes or per instructions in the treatment section of the protocol. Following administration of *nab*-paclitaxel, the intravenous line should be flushed with 0.9% sodium chloride solution for injection to ensure administration of the complete dose. **NOTE: Premedications for hypersensitivity reactions (e.g., as given for paclitaxel) are not required for *nab*-paclitaxel.**

**15.15 Pharmacokinetic Information:**

**Distribution:**  $V_d$  1741 L (extensive extravascular distribution and/or tissue binding)

**Protein binding:** 94%

**Metabolism:** Hepatic primarily via CYP2C8 to 6- $\alpha$ -hydroxypaclitaxel; also to minor metabolites via CYP3A4

**Half-life elimination:** Terminal: 13 to 27 hours

**Excretion:** Feces (~22%); urine (3.9% as unchanged drug, <1% as metabolites)

**15.16 Potential Drug Interactions:** No drug interactions studies have been conducted with Paclitaxel Protein Bound. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering Paclitaxel Protein Bound concomitantly with medicines known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, nelfinavir and clopidogrel) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

**Cytochrome P450 Effect: Substrate** (major) of CYP2C8, 3A4; **Induces** CYP3A4 (weak).

**Increased Effect/Toxicity:** CYP2C8 inhibitors may increase the levels/effects of paclitaxel.

**Decreased Effect:** CYP2C8 inducers may decrease the levels/effects of paclitaxel.

**Herb/Nutraceutical Interactions:** Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid valerian, St John's wort (may decrease paclitaxel levels), kava kava, gotu kola (may increase CNS depression).

**Immunosuppressants:** enhanced adverse/toxic effect of pimecrolimus or tacrolimus

**Tofacitinib:** enhanced effect of tofacitinib; Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants.

**Vaccines:** enhanced adverse/toxic effect of live vaccines and diminished therapeutic effect of live vaccines. Avoid use of live organism vaccines, and live-attenuated vaccines should not be given for at least 3 months after paclitaxel.

**Vinorelbine:** Paclitaxel Protein Bound may enhance the neurotoxic effect of vinorelbine.

**Avoid combination of Paclitaxel Protein Bound with:** BCG (diminished therapeutic effect of BCG), clozapine (increased risk of agranulocytosis), natalizumab (increased risk of infection), and dipyrrone (increased risk of agranulocytosis and pancytopenia).

Administration of carboplatin immediately after the completion of the *nab*-paclitaxel infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure in plasma. The observed mean half-life and clearance for total and free carboplatin in the presence of *nab*-paclitaxel were consistent with those reported in the absence of *nab*-paclitaxel. In patients with solid tumors, oral azacitidine (CC-486) had minimal to no effect on *nab*-paclitaxel PK. Similarly, *nab*-paclitaxel had minimal to no effect on PK of oral

azacitidine. Pharmacokinetic interactions between *nab*-paclitaxel and gemcitabine have not been evaluated in humans.

- 15.17 **Known potential toxicities:** Consult the investigator brochure or package insert for the most current and complete information. Adverse events may affect the ability to drive and use machines.

**Common known potential toxicities,  $\geq 10\%$ :**

**Cardiovascular:** ECG abnormal, peripheral edema

**Central Nervous System:** Peripheral sensory neuropathy, fatigue, peripheral neuropathy, headache, depression

**Dermatologic:** Alopecia, skin rash

**Endocrine & metabolic:** Dehydration, increased gamma-glutamyl transfer, hypokalemia

**Gastrointestinal:** Nausea, diarrhea, decreased appetite, vomiting, constipation, dysgeusia

**Genitourinary:** Urinary tract infection

**Hematologic & oncologic:** Anemia, neutropenia, thrombocytopenia, bone marrow depression (dose-related)

**Hepatic:** AST increased, alkaline phosphatase increased

**Infection:** Infection (oral candidiasis, respiratory tract infection, pneumonia)

**Neuromuscular & skeletal:** Weakness, musculoskeletal pain, limb pain

**Ophthalmic:** Vision disturbance

**Renal:** Creatinine increased

**Respiratory:** Cough, sputum, dyspnea

Miscellaneous: Fever

**Less Common known potential toxicities,  $\geq 1\%$  -and  $< 10\%$ :**

**Cardiovascular:** Edema, cardiac failure, hypotension, significant cardiovascular events (included chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)

**Hematologic & oncologic:** Hemorrhage, febrile neutropenia

**Hepatic:** Bilirubin increased

**Hypersensitivity:** Hypersensitivity reaction (includes anaphylactic reactions, chest pain, dyspnea, flushing, hypotension)

**Infection:** Sepsis

**Ophthalmic:** Cystoid macular edema

**Respiratory:** Pneumonitis

**Rare known potential toxicities,  $< 1\%$  (Limited to important or life-threatening):**

Atrioventricular block, autonomic neuropathy, bradycardia, cardiac arrhythmia, cerebrovascular accident, cranial nerve palsy, embolism, hepatic encephalopathy, hepatic necrosis, intestinal obstruction, injection site reaction, intestinal perforation, ischemic colitis, ischemic heart disease, left ventricular dysfunction, maculopapular rash, myocardial infarction, neutropenic sepsis, optic nerve damage (rare), palmar-plantar erythrodysesthesia (in patients previously exposed to capecitabine), pancreatitis, pancytopenia, paralytic ileus, peripheral motor neuropathy, pneumonia, pneumothorax, pruritis, pulmonary embolism, radiation

pneumonitis (with concurrent radiation therapy), radiation recall phenomenon, skin photosensitivity, Stevens-Johnson syndrome, thrombosis, toxic epidermal necrolysis, transient ischemic attacks, ventricular dysfunction, vocal cord paralysis.

**Note for Safety in Elderly Patients:** In patients 75 years and older receiving monotherapy with *nab*-paclitaxel, increased incidences were observed for clinically severe infections, dehydration, diarrhea, anemia, fatigue, and peripheral edema, while neutropenia and peripheral neuropathy were observed at a similar rate. For the combination of *nab*-paclitaxel with gemcitabine, there was an increased incidence for risk of hematologic toxicity (myelosuppression), peripheral neuropathy, dehydration, and decreased appetite. Patients aged 75 years and older should be carefully assessed for their ability to tolerate *nab*-paclitaxel in combination with gemcitabine. Special consideration should be given to performance status, comorbidities, and increased risk of infections.

In patients  $\geq 65$  years old, a higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found. Myelosuppression events, peripheral neuropathy events, arthralgia and dehydration were more frequent.

- 15.18 **Drug procurement:** Celgene will supply investigational *nab*-paclitaxel to the ACCRU coordinating center pharmacy. Each participating ACCRU main membership will order a starter supply of *nab*-paclitaxel from the research base pharmacy. Fax the ACCRU Clinical Drug Order/Return Form

to:



Each participating ACCRU main membership will be responsible for monitoring the supply of *nab*-paclitaxel and will use the ACCRU Clinical Drug Order/Return Form to order additional supplies as needed.

*Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.*

15.19 **Nursing guidelines:**

15.191 *Nab*-paclitaxel is not known to cause the hypersensitivity reactions that Taxol does, secondary to the fact that *nab*-paclitaxel lacks the Chremophor EL solvent of regular paclitaxel solution, therefore premedication is not necessary. However the patient should still be monitored closely and the infusion stopped if acute reactions occur (chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm, and/or urticaria).

15.192 Approximately 0-40% of patients may experience some degree of peripheral sensory neuropathy (numbness, tingling, burning pain,

fine motor skills impairment, paresthesias, distal sensory loss) depending on the dose and schedule used. Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses  $>170 \text{ mg/m}^2/\text{day}$  and with cumulative doses over multiple courses of therapy. The nerve damage may take days to months to resolve.

- 15.193 Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1 quart boiled water) or try OTC oral Lysine or Vitamin E.
- 15.194 Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.
- 15.195 Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.
- 15.196 Monitor liver function tests
- 15.197 Inform patient about total alopecia
- 15.198 *Nab*-paclitaxel has not been tested in combination with anthracyclines, and it is not known if there is an increased risk of cardiotoxicity.
- 15.199a Monitor IV site closely and establish patency before administration, it is uncertain whether *nab*-paclitaxel is an irritant as Taxol is.
- 15.199b Use in caution and employ additional monitoring in patients  $>75$  years of age, as increased incidence of adverse events were observed in this age group.
- 15.199c Avoid the use of live vaccines for 3 months after last dose of *nab*-paclitaxel.
- 15.199d Warn patients of the possibility of radiation recall

15.2 Bevacizumab (Avastin<sup>®</sup>)**Investigator brochure contact information:**

The most current version of the Investigator Brochure will be maintained in the study folder on the ACCRU website. Updated Investigator's Brochures should be obtained from the study folder as they become available.

Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study.

15.21 **Background:** Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.22 **Formulation:** Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

Bevacizumab is supplied in 100 mg (4 mL) and 400 mg (16 mL) glass vials, each with a concentration of 25 mg/mL. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

15.23 **Preparation and storage:** Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE.**

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. **Do not administer or mix with dextrose solution.** From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

- 15.24 **Administration:** Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Do not initiate bevacizumab for 28 days following major surgery and until surgical wound is fully healed.

Refer to Section 7 for protocol-specific administration instructions. Guidelines recommended by the manufacturer are included for reference.

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

- 15.25 **Pharmacokinetic information:**

**Distribution:**  $V_d$ : 46 mL/kg (limited extravascular distribution)

**Half-life elimination:** ~20 days (range: 11-50 days)

**Clearance:** 2.75-5 mL/kg/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.

**Time to steady state:** 100 days

- 15.26 **Potential Drug Interactions:** Overall the results from the drug-drug PK interaction investigations showed no interaction between bevacizumab and the anti-cancer agents tested. Co-administration of bevacizumab with various chemotherapeutic and other anti-cancer agents resulted in similar values of CL and  $V_c$  for bevacizumab, suggesting that the exposure of bevacizumab are not affected by concomitant dosing with doxorubicin, capecitabine, capecitabine/oxaliplatin (XELOX), 5-FU/leucovorin, 5-FU/leucovorin/irinotecan (IFL), 5-FU/leucovorin/oxaliplatin (FOLFOX4), erlotinib, carboplatin, cisplatin, oxaliplatin, paclitaxel, gemcitabine, temozolomide or interferon- $\alpha$ 2a.

The effect of bevacizumab on the disposition of several agents (doxorubicin, 5-FU, irinotecan [and its active metabolite SN38], capecitabine, oxaliplatin, carboplatin, cisplatin, paclitaxel, gemcitabine, erlotinib, temozolomide and interferon alfa-2a) has been investigated. Accumulating data do not suggest that bevacizumab affects disposition of anti-neoplastic agents.

**Increased Effect/Toxicity:** Bevacizumab may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Bevacizumab may also enhance the adverse/toxic effect of Irinotecan, Sorafenib, and Sunitinib. Sunitinib may enhance the adverse/toxic effect of Bevacizumab. Specifically, the risk for a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased.

- 15.27 **Known potential adverse events:** Consult the investigator's brochure and package insert for the most current and complete information. U.S. Boxed Warnings include severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding. Avoid use in patients with serious hemorrhage or

recent hemoptysis. Percentages reported as Monotherapy and as part of combination chemotherapy regimens.

**Common known potential toxicities, > 10%:**

Cardiovascular: Hypertension, venous thromboembolism, peripheral edema, hypotension, arterial thrombosis

Central nervous system: Fatigue, pain, headache, dizziness, taste disorder, peripheral sensory neuropathy, anxiety

Dermatologic: Alopecia, palmar-plantar erythrodysesthesia, exfoliative dermatitis, xeroderma

Endocrine & metabolic: Ovarian failure, hyperglycemia, hypomagnesaemia, weight loss, hyponatremia, hypoalbuminemia

Gastrointestinal: Abdominal pain, vomiting, anorexia, constipation, decreased appetite, diarrhea, stomatitis, gastrointestinal hemorrhage, dyspepsia, nausea

Genitourinary: Proteinuria, urinary tract infection, pelvic pain

Hematologic and oncologic: Hemorrhage, leukopenia, pulmonary hemorrhage, neutropenia, lymphocytopenia

Infection: Pneumonia, catheter infection, or wound infection

Neuromuscular and skeletal: Myalgia, back pain

Renal: Increased serum creatinine

Respiratory: Upper respiratory tract infection, epistaxis, dyspnea, rhinitis

Miscellaneous: Postoperative wound complication (including dehiscence)

**Less common known potential toxicities, 1% - 10%:**

Cardiovascular: Thrombosis, deep vein thrombosis, syncope, intra-abdominal thrombosis, left ventricular dysfunction, pulmonary embolism

Central Nervous System: Voice disorder, Dermatologic: Dermal ulcer, cellulitis, acne vulgaris.

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Xerostomia, rectal pain, colitis, intestinal obstruction, gingival hemorrhage, gastrointestinal perforation, gastroesophageal reflux disease, gastrointestinal fistula, gingivitis, oral mucosa ulcer, gastritis, gingival pain

Genitourinary: Vaginal hemorrhage

Hematologic & oncologic: Febrile neutropenia, neutropenic infection, thrombocytopenia, hemorrhage.

Infection: Tooth abscess

Neuromuscular & skeletal: Weakness, dysarthria

Ophthalmic: Blurred vision

Otic: Tinnitus, deafness

Respiratory: Pneumonitis

Miscellaneous: Gastrointestinal-vaginal fistula, anal fistula, infusion related reaction.

**Rare known potential toxicities, <1% (Limited to important or life-threatening):**

Angina pectoris, antibody development (anti-bevacizumab and neutralizing), bladder fistula, bronchopleural fistula, cerebral infarction, conjunctival hemorrhage, endophthalmitis (infectious and sterile), fistula of bile duct, fulminant necrotizing fasciitis, gall bladder perforation,

gastrointestinal ulcer, hemolytic anemia (microangiopathic; when used in combination with sunitinib), hemoptysis, hemorrhagic stroke, hypersensitivity, hypertensive crisis, hypertensive encephalopathy, increased intraocular pressure, intestinal necrosis, intraocular inflammation (iritis vitritis), mesenteric thrombosis, myocardial infarction, nasal septum perforation, ocular hyperemia, osteonecrosis of the jaw, ovarian failure, pancytopenia, polyserositis, pulmonary hypertension, rectal fistula, renal failure, renal fistula, renal thrombotic microangiopathy, retinal detachment, retinal hemorrhage, reversible posterior leukoencephalopathy syndrome, sepsis, tracheoesophageal fistula, vaginal fistula, vitreous hemorrhage, vitreous opacity.

- 15.28 **Drug procurement:** Genentech will supply commercial drug labeled for investigational use to Biologics Inc. Each participating ACCRU main membership will order the drug from Biologics Inc. Fax the Drug Order Request Form (found in the Forms folder) request to:



Each participating ACCRU main membership will be responsible for monitoring the supply of bevacizumab and will use the Drug Order Request Form to order additional supplies as needed.

*Outdated or remaining drug is to be destroyed on-site according to procedures in place at each institution..*

15.29 **Nursing guidelines:**

- 15.291 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.
- 15.292 Monitor urine dipstick or UPC as required by the test schedule
- 15.293 Evaluate IV site regularly for signs of infiltration.
- 15.294 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.
- 15.295 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

- 15.296 Patient may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.
- 15.297 Monitor for skin rash, instruct patient to report to MD.
- 15.298 Monitor blood pressure. Administer antihypertensives as ordered by MD.
- 15.299a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to MD immediately.
- 15.299b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.
- 15.299c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.
- 15.299d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.
- 15.299e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.
- 15.299f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.
- 15.299g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.
- 15.299h Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.

- 15.299i Warn female patients of the risk of rectovaginal fistula.
- 15.299j Agent may cause increased cardio toxic effects of anthracyclines as well as toxic effects of irinotecan, sorafenib, and sunitinib. Patients who are on dual therapy with these agents should be monitored closely.

### 15.3 Ipilimumab (Yervoy®)

- 15.31 **Background:** Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). CTLA-4 is a down-regulator of T-cell activation pathways. Blocking CTLA-4, allows for enhanced T-cell activation and proliferation. In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors.
- 15.32 **Formulation:** Commercially available for injection 5 mg/mL (10 mL, 40 mL). [contains diethylene triamine pentacetic acid, mannitol, polysorbate 80]
- 15.33 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature, do not freeze or shake. Protect from light. Reconstitution is not required. Appropriate dose should be added to 0.9% NaCL or D5W to a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion. Preparations in infusion containers are stable for up to 24 hours under refrigeration or at room temperature.
- 15.34 **Administration:** Administer via I.V. infusion over 90 minutes through an intravenous line containing a low-protein-binding in-line filter. Flush the intravenous line with after each dose. Do not mix ipilimumab with, or administer as infusion with, other medicinal products.
- 15.35 **Pharmacokinetic information:**  
**Distribution:**  $V_{ss}$ : 7.21 L  
**Half-life elimination:** Terminal: 15.4 days
- 15.36 **Potential Drug Interactions:** Vemurafenib: Ipilimumab may enhance the hepatotoxic effect of Vemurafenib. Management: Consider alternatives to this combination when possible. Use of this combination should only be undertaken with extra close monitoring of liver function (hepatic transaminases and bilirubin) and signs/symptoms of hepatotoxicity.
- 15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe and fatal immune-mediated adverse reactions may occur. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose.

**Common known potential toxicities, > 10%:**

Central nervous system: Fatigue, headache  
 Dermatologic: Pruritus, skin rash, dermatitis (including Stevens-Johnson syndrome, toxic epidermal necrolysis, dermal ulceration, necrosis, bullous or hemorrhagic dermatitis)  
 Endocrine & metabolic: Weight loss, pituitary insufficiency  
 Gastrointestinal: Nausea, diarrhea, appetite decreased, increased serum lipase, vomiting, constipation, colitis, enterocolitis, abdominal pain, increased serum amylase  
 Hematologic & oncologic: Anemia, decreased hemoglobin  
 Hepatic: Increased serum ALT, increased serum AST, increased serum alkaline phosphatase, increased serum bilirubin, hepatitis  
 Respiratory: Dyspnea, cough  
 Miscellaneous: Fever

**Less common known potential toxicities, 1% - 10%:**

Central nervous system: Insomnia, neuropathy  
 Dermatologic: Urticaria, vitiligo  
 Endocrine & metabolic: Hypothyroidism, hypophysitis, adrenal insufficiency  
 Gastrointestinal: Intestinal perforation, pancreatitis  
 Hematologic & oncologic: Eosinophilia  
 Hepatic: Hepatotoxicity  
 Immunologic: Antibody development  
 Renal: Increased serum creatinine, nephritis

**Rare known potential toxicities, <1% (Limited to important or life-threatening):**

Acute respiratory distress syndrome, adrenocortical insufficiency, arthritis, blepharitis, bronchiolitis obliterans organizing pneumonia, capillary leak syndrome, conjunctivitis, Cushing's syndrome, DRESS syndrome, encephalitis, episcleritis, erythema multiforme, esophagitis, gastrointestinal ulcer, giant-cell arteritis, Graves ophthalmopathy, Guillain-Barré syndrome, hemolytic anemia, hepatic failure, hepatitis (immune-mediated), hypersensitivity angitis, hypogonadism, hyperthyroidism, hypoacusis (neurosensory), increased thyroid stimulating hormone level, infusion reaction, iritis, meningitis, myasthenia gravis, myelofibrosis, myocarditis, myositis, neuropathy (sensory and motor), neurosensory hypoacusis, ocular myositis, pancreatitis, pericarditis, peritonitis, pneumonitis, polymyalgia rheumatica, psoriasis, renal failure, sarcoidosis, scleritis, sepsis, temporal arteritis, thyroiditis (autoimmune), uveitis, vasculitis.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines**

15.391 Ipilimumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team

immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

- 15.392 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- 15.393 Rash/pruritis/dermatitis is seen. Cases of Steven-Johnson Syndrome or toxic epidermal necrolysis have been reported. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.
- 15.394 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately. Use with extreme caution in combination with Vemurafenib as this may increase the hepatotoxicity of Vemurafenib.
- 15.395 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- 15.396 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- 15.397 Patients who are started on steroid therapy for any side effects of Ipilimumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
- 15.398 Monitor creatinine as nephritis may be seen.
- 15.399 Instruct patients to report any ocular symptoms (dry eyes, tearing, and/or eye pain) to the study team immediately.

## **16.0 Statistical Considerations and Methodology**

### 16.1 Background

Boasberg et al<sup>7</sup> examined the utility of the combination of *nab*-paclitaxel with bevacizumab (administered as *nab*-paclitaxel: 150 mg/m<sup>2</sup> on days 1, 8, and 15 and bevacizumab: 10 mg/ on days 1 and 15 of a 4-week cycle until disease progression or dose limiting toxicity) in chemotherapy naïve patients with metastatic melanoma. With 41 of the planned 50 patient goal of this Phase II clinical trial enrolled, median progression free survival was 6.25 months (95%CI: 5.63-9.41 months).

Hersh et al<sup>8</sup> reported the results of a randomized phase II clinical trial of Ipilimumab with or without dacarbazine in chemotherapy-naïve patients with metastatic melanoma. Of the 37 patients randomized to Ipilimumab alone administered at 3 mg/kg every 4 weeks for a maximum of 4 cycles, the median overall survival rate was 11.4 months (95% CI: 6.1-15.6 months) with a 6 month clinical benefit rate (CR, PR, or stable disease by RECIST criteria) of 10.8% . [The progression-free survival was not reported. If the 6 month clinical benefit rate is used as an approximation to the 6 month PFS rate, then median PFS is about 3.25 months).

## 16.2 Endpoint(s).

### 16.21 Primary Endpoint

The primary endpoint is progression-free survival (PFS) defined as time from randomization to the earliest documentation of progression as defined by the RECIST criteria (version 1.1) or death from any cause without the documentation of progression.

The study will test the hypothesis that there will be a 40% decrease in the hazard of disease progression with AB relative to ipilimumab (improvement in median PFS from 3 to 5 months).

### 16.22 Secondary Endpoints:

- overall survival (OS) as well as the the hazard of death among those randomized to AB then ipilimumab relative to those randomized to ipilimumab then AB
- tumor response (using the RECIST criteria)
- safety profile of each treatment reigmen

### 16.23 Descriptive correlative laboratory studies:

- Changes in biomarkers of angiogenesis (Arm A);
- Changes in biomarkers of immunity (Arms A and B);
- Pharmacokinetic changes in nab-paclitaxel plasma concentrations

## 16.3 Stratification Factors

This study will use the Pocock and Simon<sup>9</sup> dynamic allocation procedure to allocate an equal number of patients to each of the treatment strategies. This procedure will balance the marginal distributions of the stratification factors between these treatment strategies. The stratification factors that will be used are: sub-stage of disease (M1a/b vs. M1c), BRAF 600 mutation present (yes vs. not or metastatic melanoma is of uveal origin), and prior treatment in the metastatic setting (yes vs. no) (see Section 5.0).

#### 16.4 Sample size with power justification.

This study was designed to detect a 40% decrease in the hazard of disease progression with AB relative to IPI (improvement in median PFS from 3 to 5 months). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for PFS and OS endpoints.

Sample sizes were determined under the assumptions that: (1) the accrual rate would be 4-5 eligible patients per month over 24 months, 2) the follow-up period after accrual is terminated will be 12 months, 3) the distributions of PFS times for each treatment regimen follow an exponential distribution, and 4) the hazard rates are proportional, and the median PFS time with ipilimumab would be 3.0 months.

With a sample size of 53 eligible patients per treatment arm, a one-sided  $\alpha=0.10$  log rank test would have 90% power to detect a 40% decrease in the hazard of disease progression in the better arm when the hazard of disease progression in the poorer arm is 0.2310. This is equivalent to an increase in the median PFS from 3 months to 5 months. The expected number of progression and deaths without progression at the time of the final analysis is 101.

The trial will be reviewed by the MCC DSMB every 6 months. The study statistician will monitor the trial assumptions (including accrual and event rate in the standard treatment arm) as well as safety and recommend changes to the DSMB if assumptions do not appear appropriate or excessive toxicity is encountered.

To account for patients who cancel participant prior to the start of treatment or are found to be ineligible, the sample size will be increased by 5%. Thus, we anticipate enrolling a minimum of 106 or a maximum of 112 patients.

#### 16.5 Analysis plan

All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for assessment of all of the clinical endpoints. Patients will be included in the treatment group they were randomized to regardless of their actual treatment or duration of treatment. Summary statistics for patient and tumor characteristics, eligibility rates, length of follow-up, and treatment acceptance rates will be calculated by assigned treatment arm.

##### 16.51 Progression-free and overall survival

Progression-free survival time is defined as the time from randomization to documentation of first disease progression or death due to any cause. Survival time is defined as the time from registration to death due to any cause.

The distributions of OS times and PFS times for each treatment arm will be estimated using the Kaplan-Meier method. A stratified log-rank test and Cox partial likelihood score test will be used to assess whether the distribution of OS times or PFS times differ with respect to treatment arm having adjusted for M stage (M1c vs. else), , and presence of BRAF 600 mutation. For OS and PFS, Cox modeling with the partial likelihood score tests will be used to examine the

strength of association between these time to event distributions and additional potential prognostic factors.

#### 16.52 Tumor response rate

Tumor response is defined as complete or partial response (using RECIST criteria on 2 consecutive evaluations at least 8 weeks apart. The first line ipilimumab tumor response rate will be determined among all patients who meet the eligibility criteria, were randomized to Arm B, and began treatment. The second line ipilimumab tumor response rate will be determined among all patients who meet the eligibility criteria, who were randomized to Arm A, progressed on AB, and began ipilimumab treatment. The first and second line response rates with AB similarly defined.

#### 16.53 Safety Profile

Adverse events will be graded and attribution assigned using CTC CAE version 4.0. For each type of toxicity reported, the proportion of patients on each treatment arm experiencing a severe level of that toxicity will be determined. For each agent, the total dose delivered as a percentage of the starting dose will be determined.

- 16.6 This randomized phase II clinical trial will be monitored by the Mayo Clinic Cancer Center Data and Safety Monitoring Board (MCCC DSMB). The study statistician will prepare a report containing accrual and adverse event that will be submitted to MCCC DSMB every 6 months. Efficacy data will be submitted to the MCCC DSMB at the planned interim analyses .

#### **Safety Stopping rules:**

Enrollment to this clinical trial will be temporarily suspended if any of the following occurs:

- 3 or more of the first 15 patients randomized to Arm A or 25% or more of the patients randomized to Arm A thereafter develop a grade 4 or 5 non-hematologic toxicity considered possibly, probably, or definitely related to treatment during their 4 cycles of IpI treatment
- 3 or more of the first 15 patients randomized to Arm B or 25% or more of the patients randomized to Arm B thereafter develop a grade 4 or 5 non-hematologic toxicity considered possibly, probably, or definitely related to treatment during the first 3 cycles of BEV + nab-paclitaxel treatment

Crossover from IpI to BEV + nab-paclitaxel will be temporarily suspended if any of the following occurs:

- 3 or more of the first 15 patients who crossover to BEV + nab-paclitaxel or 25% or more of the patients who crossover to BEV + nab-paclitaxel thereafter develop a grade 4 or 5 non-hematologic toxicity considered possibly, probably, or definitely related to treatment during the first 3 cycles of BEV + nab-paclitaxel treatment

Crossover from BEV + nab-paclitaxel to IpI will be temporarily suspended if any of the following occurs:

- 3 or more of the first 15 patients who crossover to IpI or 25% or more of the patients who crossover to IpI thereafter develop a grade 4 or 5 non-hematologic toxicity considered possibly, probably, or definitely related to treatment during their 4 cycles of IpI treatment

The study team will review all adverse event data. A trial recommendation will be formulated and presented to the MCCC DSMB – the study may permanently close or may re-open to accrual after MCCC DSMB review and IRB approval of protocol/consent form modifications.

#### **Futility Analysis:**

After the 50% of the patients have reported progression of disease (80 events), a futility analysis will be conducted to examine whether it is highly unlikely that the AB regimen would yield statistically significant results in its favor at the end of the study. The findings of this analysis will be reported to the DSMB. The conditional probability (CP) of rejecting  $H_0$  at the end of the study given the PFS data at the study time point where 50% of the total number of progressions required for the final analysis has occurred will be calculated using the CP formulas found in Proschan et al (10) as well as Jitlal et al (11). If the CP is found to be  $\leq 15\%$  (10), consideration will be given to recommending to the DSMB the termination of trial enrollment.

#### **Interim Efficacy Analysis:**

Formal comparisons of PFS will be made when approximately 75% and all of the expected number of events have occurred for that comparison. The Lan-DeMets method for computing discrete sequential two-sided boundaries with an alpha spending function yielding O'Brien-Fleming type boundaries (12) will be used to account for sequential testing and to maintain the overall preset type I error rate of 0.05. The alpha levels for the interim analyses and final analysis are 0.0193, and 0.0307, respectively.

16.7 Inclusion of Women and Minorities

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	45	66	111
<b>Ethnic Category: Total of all subjects*</b>			
Racial Category			
American Indian or Alaskan Native			
Asian			
Black or African American			
Native Hawaiian or other Pacific Islander			
White	45	67	112
<b>Racial Category: Total of all subjects*</b>	45	67	112

**Ethnic Categories:** **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

**Not Hispanic or Latino**

**Racial Categories:** **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

**Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

**Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

**17.0 Pathology Considerations/Tissue Biospecimens**

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

<b>Type of tissue biospecimen to submit</b>	<b>Mandatory or optional</b>	<b>When to submit</b>	<b>Reason for submission (background/methodology section)</b>	<b>Where to find specific details for biospecimen submission</b>
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (OR 10 five-micron unstained slides with corresponding H&E)	Optional	≤30 days after registration/randomization	Correlative studies (Section 17.3)	Section 17.2

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from metastatic tumor biopsy.

17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut (10) five micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** H&E stain every 10<sup>th</sup> slide (i.e., slides labeled 1, 10). These H&E slides will be reviewed centrally under the research base’s protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.3. For samples containing less than 1-2 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides. Do not use sticky labels on the slides.**

- 17.23 If a specimen is to be submitted the following materials below are mandatory (unless indicated otherwise) and required for shipment:
- Paraffin embedded tissue blocks with corresponding H&E slide (OR 10 unstained slides with corresponding H&E).
  - Research Tissue Specimen Submission Form
  - Surgical Pathology Report
  - Operative Report (*optional*)

**Note: Please include the ACCRU patient ID number on all materials listed above.**

- 17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.
- 17.25 Metastatic tissue specimens must be shipped  $\leq 30$  days after registration/randomization.
- 17.26 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).
- 17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:



- 17.28 If a corresponding H&E wasn't submitted with the block/slides, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and forwarded to *Dr. Lori Erickson/ and colleagues* to be reviewed under the research base's protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed.

When an appropriate request is submitted, the ACCRU Operations Office will forward the block/slides to the ACCRU Research Base PRC, Mayo Clinic Rochester (Attn: PRC) for processing as outlined in Section 17.32.

### 17.3 Study Methodology and Storage Information

- 17.31 Submitted tissue samples will be analyzed as follows: FFPE tumor tissue blocks/slides (10 unstained slides) will be collected in order to assess correlation

of responses to treatment with tumor infiltrating lymphocytes (CD3, CD8, CD4) and levels of VEGF expression by tumor cells. Both measurements will be semi-quantitatively assessed by established immunohistochemistry (IHC) methodology in our laboratory.

- 17.32 Definitive immunohistochemical analysis using optional US-guided core needle tumor biopsies will be performed at the end of the study, comparing pre-treatment measurements (see 17.41) with changes at time of tumor progression on therapy.
- 17.4 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (Attn.: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.15). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.
- 17.5 Banking of tumor tissue, according to the patient consent permission (see Section 6.15), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU melanoma studies.)
- 17.6 The institutional pathologist will be notified by Michael Thompson in Dr. Markovic's Hematology/Oncology laboratory if the block may be depleted.
- 17.7 Blocks requested to accommodate individual patient management will be returned promptly upon request.
- 17.8 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient re-consent is required.

**18.0 Records and Data Collection Procedures**

18.1 Submission Timetable



**Initial Material(s)**

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration/randomization
Baseline Adverse Event Form	
RECIST Measurement Form -Baseline	
Tumor Imaging Submission Form <sup>1</sup>	
Research Tissue Submission Form (see Section 17.0)	
OP and Path Reports (see Section 17.0) <sup>2</sup>	Submit ≤2 weeks after registration/randomization if withdrawal/refusal occurs prior to beginning protocol therapy
End of Active Treatment/Cancel Notification Form	

1. Excluding brain MRI and/or CT scan of the head with contrast, images taken during the study should be submitted via CD ≤ 2 weeks after they are obtained (see Appendix III).
2. Submit a copy to the ACCRU Ops Office, either electronically to



This is in addition to the pathology material requirements for tissue submission ( Section 170.)

**Test Schedule Material(s)**

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)			
	At each evaluation during treatment	Observation period after completion of 4 cycles of Ipi	At end of AB treatment as well as end of Ipi treatment	At progression during any treatment or observation phase
Evaluation/Treatment Form	X <sup>2</sup>		X <sup>2</sup>	
Evaluation/Observation Form		X <sup>3</sup>		
Adverse Event Form	X	X	X	
RECIST Measurement Form	X	X	X <sup>1</sup>	
Tumor Imaging Submission Form <sup>4</sup>		X <sup>8</sup>	X <sup>9</sup>	X <sup>10</sup>
Research Blood Submission Form (Mayo Clinic Rochester only)	X <sup>7</sup> (see Section 14.0)			
End of Initial Treatment Form			X <sup>5</sup>	
End of (ALL) Active Treatment/Cancel Notification Form			X <sup>6</sup>	

1. Submit copy of documentation of response or progression either electronically to 
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Complete at each evaluation during Observation (see Section 4.0).
4. Images taken during the study should be submitted on CD (see Appendix II for imaging guidelines and Appendix III for image submission process).
5. Complete at end of Initial Treatment, even if not moving to crossover treatment.
6. Complete at end of ALL treatment.
7. Prior to the first cycle of Ipilimumab and prior to the first cycle of BEV/nab-paclitaxel.
8. Patients who discontinue AB treatment phase or the Ipi treatment phase for reasons other than progression, all tumor images taken prior to and at the time of treatment discontinuation should be submitted.
9. Patients who discontinue observation period after Ipi treatment for reasons other than progression, all tumor images taken prior to and at the time of discontinuation should be submitted.
10. Submit all tumor images taken prior to and at time of disease progression

**Follow-up Material(s):**

CRF	Event Monitoring Phase <sup>1</sup>				
	q 6 months until death or a maximum of 3 years post registration/ registration	Post treatment monitoring phase	If patient entered event monitoring phase without having progressed on both ABI007/BEV and Ipi, at first PD during event monitoring.	Death	New Primary
Event Monitoring Form	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X	At first occurrence

1. If a patient entered the event monitoring phase less than 3 years after registration, no further follow-up is required 3 years post-registration. If the patient entered the event monitoring phase 3 or more years post registration, then a single event monitoring CRF is to be completed and no further follow-up is required.
2. Submit copy of documentation of progression (clinical notes, imaging reports, pathology reports, etc.) to the [REDACTED]

**19.0 Budget**

- 19.1 Costs charged to patient: Routine clinical care costs will be the responsibility of the patient and/or the patient’s insurance company. This includes costs associated with the administration of the study drugs. Ipilimumab will be obtained through commercial suppliers.
- 19.2 Other budget concerns:
  - 19.21 Nab-paclitaxel will be provided to patients by Celgene at no charge.
  - 19.22 Bevacizumab will be provided to patients by Genentech at no charge.
- 19.3 Tests to be research funded: Research blood and tissue tests will be funded by Celgene. These include the following tests.
  - **Mayo Clinic Rochester only:** Pharmacodynamic changes of blood biomarkers of angiogenesis and immunity (see Section 14.0).

## 20.0 References

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12. Lan KKG and DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70(3):659-63, 1983.