May 24, 2019

[redacted] MS RAC
[redacted]

Dear [redacted]:

Enclosed is Addendum #13 to E3612, *A Randomized Phase II Trial of Ipilimumab with or Without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma*.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

Full IRB review of this addendum is **recommended**, however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol. It is the decision of the local IRB whether or not subjects are to be re-consented.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

The following revisions to E3612 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	Section 5.2	Add a note for Adverse Event Reporting Requirements to clarify use of CTCAE version 5.0.
3.	Section 5.3	Updated the CAEPR for Ipilimumab to Version 2.10, March 29, 2019.

The following revisions to E3612 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover page	Updated version date.
2.	"Risks and side	Updated the Risk List for Ipilimumab to Version 2.10, March 29, 2019.

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	effects related to the ipilimumab include those which are"	

If you have any questions regarding this addendum, please contact [redacted] or 857-504-2900.

We request review and approval of this addendum to E3612 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

[redacted]

[redacted]

Enclosure

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

E3612

A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

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Version Date: May 24, 2019
NCI Update Date: September 24, 2013

STUDY PARTICIPANTS

Rev. 8/14

US Sites Only
SWOG / SWOG
NRG / NRG Oncology Foundation, Inc
ALLIANCE / Alliance for Clinical Trials in Oncology

ACTIVATION DATE

December 13, 2013

PRE-ACTIVATION DATE

September 26, 2013
Addendum #1 - Incorporated Prior to Activation
Update #1- Incorporated Prior to Activation
Addendum #2 - 8/14
Addendum #3 - 10/14
Addendum #4 - 5/15
Addendum #5 – 3/16
Addendum #6 – 11/16
Addendum #7 – 2/17
Addendum #8
Addendum #9
Addendum #10

Agents	IND#	NSC#	Supply
Ipilimumab	[redacted]	732442	NCI-Supplied
Bevacizumab	[redacted]	704865	NCI-Supplied

Table of Contents

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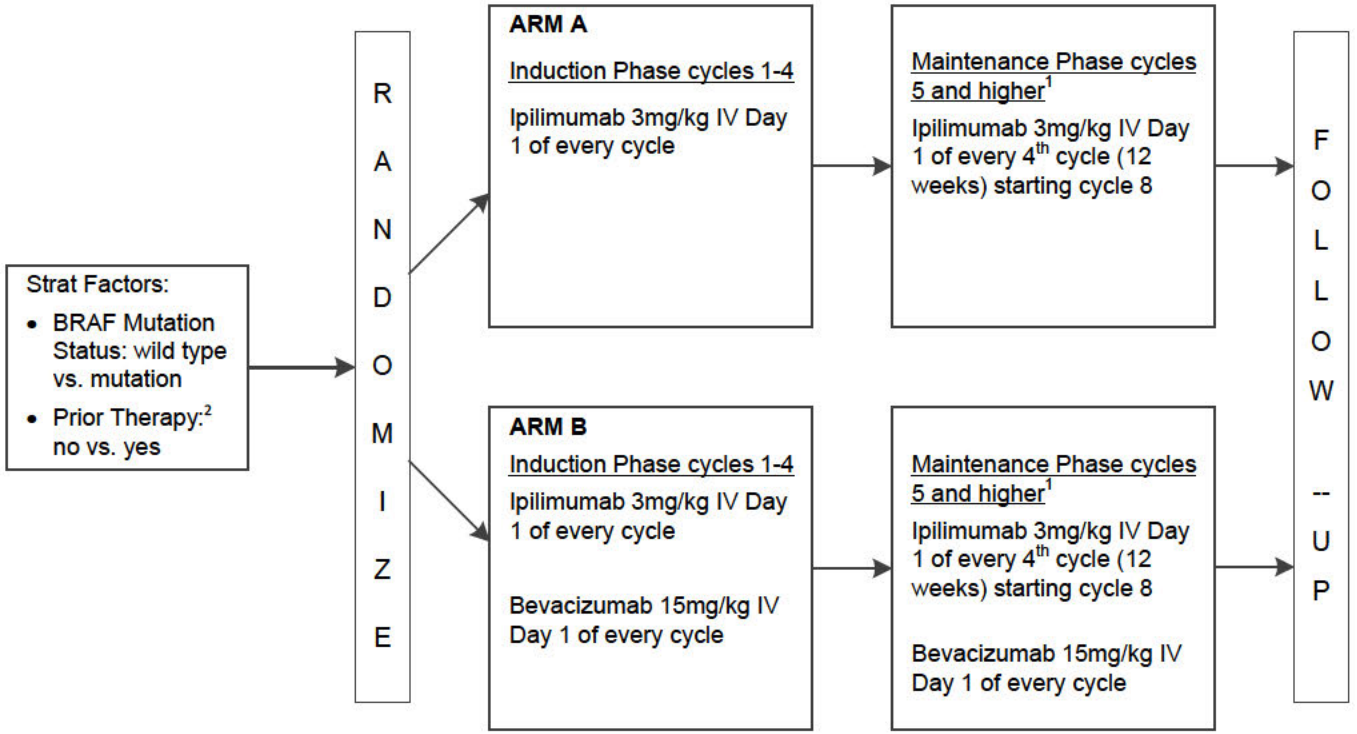
Rev. 8/14
Rev. 11/16

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via: **ONLINE**: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) **EMAIL**: CTSURegulatory@ctsu.coccg.org (regulatory documentation only) **FAX**: 215-569-0206 **MAIL**: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 For regulatory questions call the CTSU Regulatory Help Desk at 1-866-651-CTSU	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related questions) Contact the Study PI of the lead protocol organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

Rev. 5/15

Schema



Cycle=21 days
Accrual Goal: 168

1. Maintenance until excessive toxicity, progression or determination that treatment is no longer clinically beneficial
2. Prior systemic therapies for unresectable stage III or IV melanoma

1. Introduction

1.1 Research Hypothesis

Ipilimumab has been shown to prolong survival in patients with metastatic melanoma. Means to improve upon this foundation of clinical benefit for patients are worthy of pursuit. Experience thus far suggests that the combination of bevacizumab plus ipilimumab can result in enhanced immune activation with clinical benefits for patients. The adverse events have been easily managed. Given our preliminary data so far including clinical outcomes, immune activation, and pathologic evaluations of post-treatment biopsies, the ability to make a definitive assessment of clinical benefit regarding the addition of bevacizumab to ipilimumab would best be performed in a prospective, randomized fashion.

1.2 Disease Background

In the United States, 60,000 patients will be discovered to have cutaneous melanoma and of these 8,300 patients will succumb [1]. The disease will account for 4% of all new cancers and 1.4% of all cancer deaths. The neoplasm is the second and third most frequently diagnosed cancer from birth to age 39 in females and males, respectively. As a result, melanoma has a significant impact in the loss of expected years of life from cancer. Moreover, with an annual incidence increasing at 4% per year[2], the largest of any cancer type, an individual's lifetime risk for developing melanoma in the United States is currently greater than 1 in 55.

Surgical excision of melanoma is curative for most patients who present with relatively thin lesions (<1.0 mm)[3]. Those with melanoma limited to the primary site show a ten-year survival ranging from 60-90%, with the prognosis most strongly correlated with the primary tumor thickness[4]. For patients with lymph node metastases, adjuvant therapy with α-interferon affords a modest increase in overall survival, but this advantage is associated with substantial toxicities[5-8]. Dacarbazine is the most active single chemotherapy agent for disseminated disease, but complete responses are infrequent and of short duration[9]. High dose interleukin-2 (IL-2) offers a 15% response rate with approximately a 3% durable complete response rate in selected patients[10].

Recently, the use of a selective BRAF inhibitor vemurafenib has shown to offer a survival advantage in patients whose tumors harbor BRAF mutations in the front line setting with a 63% reduction of death[11]. The median progression-free survival for patients receiving BRAF inhibitors approximates 7 months. CTLA-4 blockade with ipilimumab has been shown to provide a survival advantage when compared to a peptide vaccine in previously treated patients[12] or in conjunction with dacarbazine in comparison to dacarbazine alone in the front line setting[13]. A subset of patients receiving ipilimumab experience durable clinical benefit lasting many months to years. As a result, it becomes increasingly important to build upon these successes with rational combinatorial approaches.

Preliminary results of Phase I combination study of iilimumab plus bevacizumab.

We have conducted a phase I study testing the combination of ipilimumab plus bevacizumab in patients with unresectable stage III or stage IV melanoma. To date, twenty-two patients have been enrolled (5 patients to cohort 1 (ipilimumab

10 mg/kg plus bevacizumab 7.5 mg/kg), 5 patients to cohort 2 (ipilimumab 10 mg/kg plus bevacizumab 15 mg/kg), and 12 patients in dose expansion of cohort 2) and are evaluable. There have been 6 confirmed partial responses, 1 complete response, and 7 patients who experienced prolonged stable disease of 6 months or more in duration. The median follow-up is currently 14 months, with a 6-month PFS of 59% (95% CI 36-76%, and a 1-year OS of 72% (95% CI 48-86%).

Adverse events to date have included: hypophysitis (5) and thyroiditis (3) that have been easily managed medically, one patient developed grade 2 colitis and giant cell arteritis (occurring at week 14, and with the patient experiencing a durable partial response continuing for greater than 6 months), grade 4 hepatitis (1), and uveitis/retinitis (2).

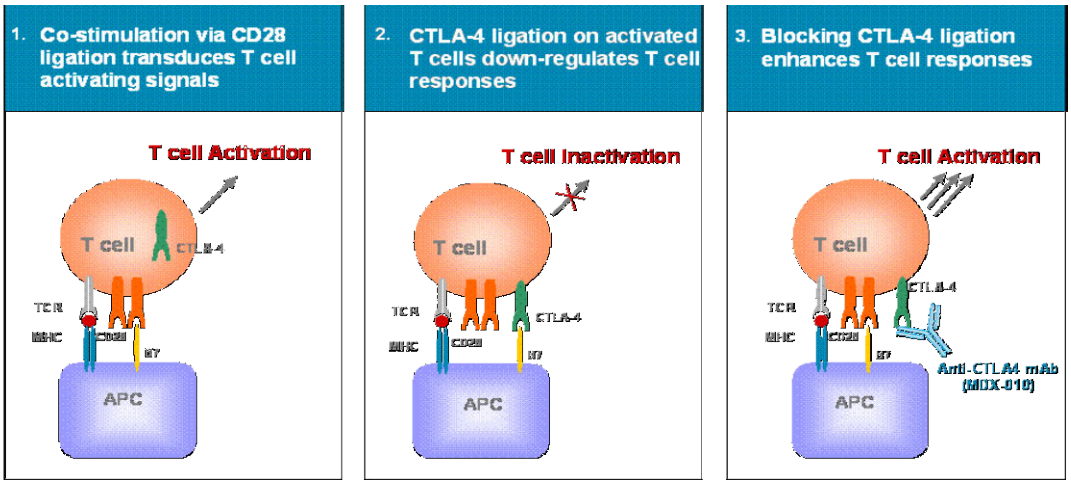
Monitoring of the peripheral blood mononuclear cells has revealed a statistically significant increase in the $CCR7^{+}/CD45R)^{+}$ and $CCR7^{-}/CD45RO^{+}$ phenotypes for both CD4 and CD8 cells as a function of treatment with ipilimumab and bevacizumab. These changes were not observed in a comparative cohort of patients who received ipilimumab alone.

Post-treatment biopsies. We have obtained biopsies of pre-existing sites of disease post-treatment in 12 patients date. Pathologic examination has revealed marked activation of the tumor vascular endothelium with brisk perivascular trafficking of tumor infiltrating lymphocytes. Post-treatment biopsies reveal brisk extravasation of tumor infiltrating lymphocytes surrounding tumor blood vessels. The vascular endothelium is columnar and are morphologically activated, similar to that seen in the high endothelia of lymph nodes representing areas of active lymphocyte trafficking with upregualtion of E-selection. There is also pathologic evidence for peripheral angiogenic T-cell recruitment.

From the phase I experience with ipilimumab plus bevacizumab, treatment is safe and tolerable with adverse events reversible. The combination has demonstrated activity in metastatic melanoma.

1.3 CTLA-4 and T Cell Activation

Figure 1 Mechanism of Action



Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors,

including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this costimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC).[14, 15] (Figure 1.)

Expression of B7 has been shown to be limited to “professional” antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs. The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.[16, 17]

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product[16, 17].

In the past few years it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28.[17] Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses.[16]

This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses; (2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune response to peptide antigens or superantigens in mice.[16-19] Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro[19].

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation.[16-18] CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell

expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.[20]

1.4 Summary of Results of Investigational Program

1.4.1 Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

1.4.2 Animal Toxicology of Ipilimumab

The effects of ipilimumab on prenatal and postnatal development in monkeys have not been fully investigated. Preliminary results are available from an ongoing study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/-), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/- heterozygous offspring. Mated CTLA-4+/- heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4-/-). The CTLA-4-/- homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3–4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The in vitro studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of

antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub-chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

1.4.3 Clinical Pharmacology

1.4.3.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

1.4.3.1.1 Pharmacokinetics of Ipilimumab

The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C max), trough concentration (Cmin), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of ipilimumab administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population pharmacokinetic analysis:

terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab Cmin achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma

cell line. Mean plasma concentrations of ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of ipilimumab. There was moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC(0-21d), 20% to 59% in CL, and 17% to 46% in Vss.

Ipilimumab was originally produced and purified from a hybridoma clone. Ipilimumab drug substance is currently manufactured using Process B. A new drug substance manufacturing process (Process C) has been developed utilizing a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps. The new drug substance manufacturing process is intended to replace the current drug substance manufacturing process. The biocomparability of Process C relative to Process B was assessed in Study CA184087.

PK in Phase 1 Study CA184087 (Process B and Process C)

The PK of ipilimumab was assessed when manufactured by a newer process C relative to current process B as an IV infusion (1.5-hr), in subjects with advanced melanoma (CA184087). Upon meeting eligibility criteria, subjects were randomized (1:1) to receive either ipilimumab Process B (Arm A, reference) or ipilimumab Process C (Arm B, test) at a dose of 10 mg/kg IV administered

over 90 minutes every 3 weeks on Days 1, 22, 43, and 64 (Weeks 1, 4, 7, and 10) during induction therapy. Randomization was stratified by baseline body weight (BW) and LDH values since both were identified as potential covariates in a population PK assessment.

The primary endpoint of PK data at week 4 demonstrated that the PK of Process B and Process C are biocomparable as the 90% CIs for the ratio of geometric means of AUC(0-21d) and Cmax - both adjusted or not adjusted for covariates - were entirely contained with the pre-specified equivalence interval (80 - 125%).

Population Pharmacokinetics

The population pharmacokinetics (PPK) of ipilimumab was developed with 420 subjects (1767 serum concentrations) with advanced melanoma in phase 2 studies (CA184007, CA184008, and CA184022). Subsequently, the final PPK model was evaluated by an external model validation dataset from CA184004 (79 subjects with 328 serum concentration data). The PPK analysis demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant. The ipilimumab CL of 15.3 mL/h from PPK analysis is consistent with that determined by PK analysis as assessed in MDX010-15 as 12.8 mL/h for a dose of 2.8 mg/kg and 15.7 mL/h for a dose of 10 mg/kg. The terminal half-life and Vss of ipilimumab calculated from the model were 14.7 days, and 7.21 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central and peripheral compartment were found to be 4.16 and 3.22 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab was found to increase with increase in body weight, supporting dosing of ipilimumab based on a weight normalized regimen. Other covariates had effects that

were either not statistically significant or were of minimal clinical relevance.

1.4.4 Clinical Safety with Ipilimumab

1.4.4.1 Overview of Clinical Trials Experience with Ipilimumab

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to ipilimumab 3 mg/kg for four doses given by intravenous infusion in previously treated patients with unresectable or metastatic melanoma was assessed in a randomized, double-blind clinical study (MDX010-20). One hundred thirty-one patients (median age 57 years, 60% male) received ipilimumab as a single agent, 380 patients (median age 56 years, 61% male) received ipilimumab with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range 1 to 4 doses). Ipilimumab was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions (≥ 5%) in patients who received ipilimumab at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 1 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the ipilimumab-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events.

Table 1: Selected Adverse Reactions in MDX010-20						
	Percentage (%) of Patients[a]					
	YERVOY 3 mg/kg n = 131		YERVOY 3mg/kg + gp100 n = 380		gp100 n = 132	
System Organ Class/Preferred Term	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorders						
Pruritus	31	0	21	< 1	11	0
Rash	29	2	25	2	8	0
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

[a] Incidences presented in this table are based on reports of adverse events regardless of causality.

Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from MDX010-20.

Table 2: Severe to Fatal Immune-mediated Adverse Reactions in MDX010-20		
	Percentage (%) of Patients	
	YERVOY 3 mg/kg n = 131	YERVOY 3 mg/kg + gp100 n = 380
Any Immune-mediated Adverse Reaction	15	12
Entercolitis [a,b]	7	7
Hepatotoxicity [a]	1	2
Dermatitis [a]	2	3
Neuropathy [a]	1	< 1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	< 1
Meningitis	0	< 1
Nephritis	1	0
Eosinophilia [c]	1	0
Pericarditis [a,c]	0	< 1

[a] Including fatal outcome

[b] Including intestinal perforation

[c] Underlying etiology not established

Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg or placebo for cycles 1-4 and as maintenance after completion of chemotherapy. Ipilimumab AEs were consistent with previous studies and predominately affected skin, GI tract, liver, and the endocrine system. Events were managed with established guidelines and were generally responsive to dose interruption/discontinuation, corticosteroids and/or other immunosuppresants. Select adverse events associated with the mechanism of action of ipilimumab, regardless of attribution by the investigator) are shown in Table 3.

Table 3: CA184024 Select Adverse Events				
	Ipilimumab + DTIC n = 247		Placebo + DTIC n = 251	
	Total	Grade 3 - 4	Total	Grade 3 - 4
	% Patients			
Dermatologic				
Pruritis	29.6	2.0	8.8	0
Rash	24.7	1.2	6.8	0
Gastrointestinal (GI)				
Diarrhea	36.4	4.0	24.7	0
Colitis	4.5	2.0	0.4	0
GI perforation	0	0	0	0
Hepatic				
Increased ALT	33.2	21.9	5.6	0.8
Increased AST	29.1	18.2	5.6	1.2
Endocrine				
Hypothyroidism	1.6	0	0.4	0
Autoimmune thyroiditis	0.8	0	0	0
Hyperthyroidism	0.4	0	0.4	0
Hypophysitis[a]	0	0	0	0

[a] 1 (0.4%) hypophysitis was reported on Day 364.

Table 4: Summary of irAE Safety Data for 10 mg/kg in Melanoma				
	Total	Low-grade (Grade 1 - 2) (%)	High-grade (Grade 3 - 4) (%)	Median Time to Resolution of Grade 2 - 4 irAEs (weeks)
All irAEs	72.3	46.2	25.2	-
Skin (eg, rash, pruritus)	52.0	49.2	2.8	6.14
GI (eg, colitis, diarrhea)	37.2	24.9	12.3	2.29
Liver (eg, LFT elevations)	8.0	0.9	6.8	4.0
Endocrine (eg, hypophysitis, hypothyroid)	6.2	3.7	2.5	20.1

Overall, the 10 mg/kg had an acceptable safety regimen, while being the most active dose. The study drug related deaths across the program are in Section 5 of the investigators brochure.

Across clinical studies that utilized ipilimumab doses ranging from 0.3 to 10 mg/kg, the following adverse

reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

1.4.4.2 Immunogenicity of Ipilimumab

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ipilimumab with the incidences of antibodies to other products may be misleading.

1.4.4.3 Pregnancy Outcomes

Based on animal data, ipilimumab may cause fetal harm. The use of ipilimumab during human pregnancy has not been formally studied in clinical trials. There have been 7 known pregnancies during ipilimumab treatment: in 3 female subjects and in the partners of 4 male study subjects. Two (2) of the 3 female pregnancies ended with elected terminations. The third female subject had a history of [redacted]. Although these outcomes do not indicate that stillbirths or other severe abnormalities will occur, pregnancy should be avoided during treatment with ipilimumab.

1.4.4.4 Immune-mediated Adverse Reactions with Ipilimumab.

Ipilimumab can result in severe and fatal immune-mediated reactions due to T-cell activation and proliferation.

Immune-related Gastrointestinal Events

The clinical presentation of GI immune-related AEs included diarrhea, increase in the frequency of bowel movements, abdominal pain, or hematochezia, with or without fever. Fatalities due to GI perforation have been reported in clinical trials of ipilimumab. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea, or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Immune-related Hepatotoxicity

Hepatic immune-related AEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis. Elevations in liver function tests (LFTs) may develop in the absence of clinical symptoms. Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

Immune-related Skin Toxicity

Skin immune-related AEs presented mostly as a rash and/or pruritus. Some subjects reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

Immune-related Endocrinopathy

Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, and adrenal insufficiency and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and

hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy. It is possible that long-term hormone replacement therapy will be required for subjects developing hypophysitis/hypopituitarism after treatment with ipilimumab.

Immune-related Neurological Events

Neurological manifestations included muscle weakness and sensory neuropathy. Fatal Guillain-Barré syndrome has been reported in clinical trials of ipilimumab. Patients may present with muscle weakness. Sensory neuropathy may also occur. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, and medications should be excluded.

Other Immune-related AEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed immune-related AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for < 1% of subjects.

Overall, immune-related AEs commonly started within 3 to 10 weeks from first dose, were successfully managed in most instances by omitting doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned above and detailed in Section 5.4.1. Immune-related AEs generally resolved within days to weeks in the majority of subjects.

1.4.5 Clinical Efficacy of Ipilimumab in Melanoma

The clinical efficacy of ipilimumab as a single agent at a dose of 3 mg/kg administered every 3 weeks for 4 doses has been established in MDX010-20 (a randomized, controlled study in second line, locally advanced/metastatic melanoma), which led to approval of ipilimumab by the FDA for the treatment of unresectable or metastatic melanoma. In study CA184024, the addition of 10 mg/kg ipilimumab to dacarbazine led to a prolongation of overall survival in patients with

previously untreated melanoma and was feasible with an acceptable safety profile.

Overall survival and other efficacy endpoints were assessed in ipilimumab studies.

Overall Survival: Prolongs survival in patients with metastatic melanoma who have failed prior treatment.

Best Objective Response Rate (BORR): By the conventional mWHO criteria confirmed objective responses have been observed in subjects receiving ipilimumab. These responses tend to be durable with the majority of subjects who achieve objective responses progression-free at the end of long observation periods.

Disease Control Rate (DCR): Disease stabilization in subjects receiving ipilimumab is a key characteristic of anti-tumor activity. Stable disease, sometimes of long duration, or slow steady decline of tumor lesion size over long periods of time, has been observed. Consequently, SD as well as objective responses (both captured in DCR) are important for completely characterizing anti-tumor activity of ipilimumab

Progression-Free Survival (PFS): Some subjects demonstrate initial tumor volume increase before response, possibly due to T-cell infiltration as shown by biopsies. Consequently, PFS incompletely captures all patterns of activity and may underestimate the clinical activity of ipilimumab.

1.4.5.1 Rationale for Using Immune-Related Tumor Assessment Criteria (irRC)

Ipilimumab is an immuno-stimulating antibody with evidence of anti-cancer activity (durable objective response and stable disease) in subjects with advanced melanoma, including subjects with established brain disease. Observations of clinical activity defined by tumor response endpoints defined by conventional criteria (eg, mWHO) may be inadequate to realize the kinetics and magnitude of clinical benefit achieved with ipilimumab.

Histopathologic evidence has demonstrated ipilimumab can produce an influx or expansion of tumor infiltrating lymphocytes. Therefore, early increases in lesion size detected radiologically or upon gross examination could be misinterpreted as progressive tumor growth and precede objective tumor shrinkage. In addition the appearance of new lesions may have categorized a subject to have progressive disease using conventional tumor assessment criteria despite the concurrent observation of objective tumor responses in pre-existing lesions and a net reduction in global tumor burden that includes the new lesions.

Hence the appearance of new lesions in and of themselves may not necessarily constitute progressive

disease. The immune-related response criteria (irRC) were developed as a tool to gauge tumor response using the changes in global tumor burden. In addition, the irRC may be useful to inform a physician's decision to continue dosing in subjects who may receive benefit from additional ipilimumab therapy. The ir-response assessment is based solely on objective measurements (SPD) of index and new lesions. Non-index lesions are not considered.

1.4.5.2 MDX010-20 (Phase 3, 3 mg/kg, previously treated melanoma)

MDX010-20, a randomized (3:1:1), double-blind, double-dummy study included 676 randomized subjects with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 subjects, 403 were randomized to receive ipilimumab at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded subjects with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Ipilimumab/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. Assessment of tumor response was conducted at Weeks 12 and 24, and every 3 months thereafter. Subjects with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the ipilimumab + gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the ipilimumab + gp100 arm compared to the ipilimumab arm, OS in the ipilimumab arm compared to the gp100 arm, best overall response rate (BORR) at Week 24 between each of the study arms, and duration of response.

Of the randomized subjects, 61%, 59%, and 54% in the ipilimumab + gp100, ipilimumab, and gp100 arms, respectively, were men. Twenty-nine (29%) percent were ≥ 65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin and 38% had elevated

LDH level. Sixty-one (61%) percent of subjects randomized to either ipilimumab -containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

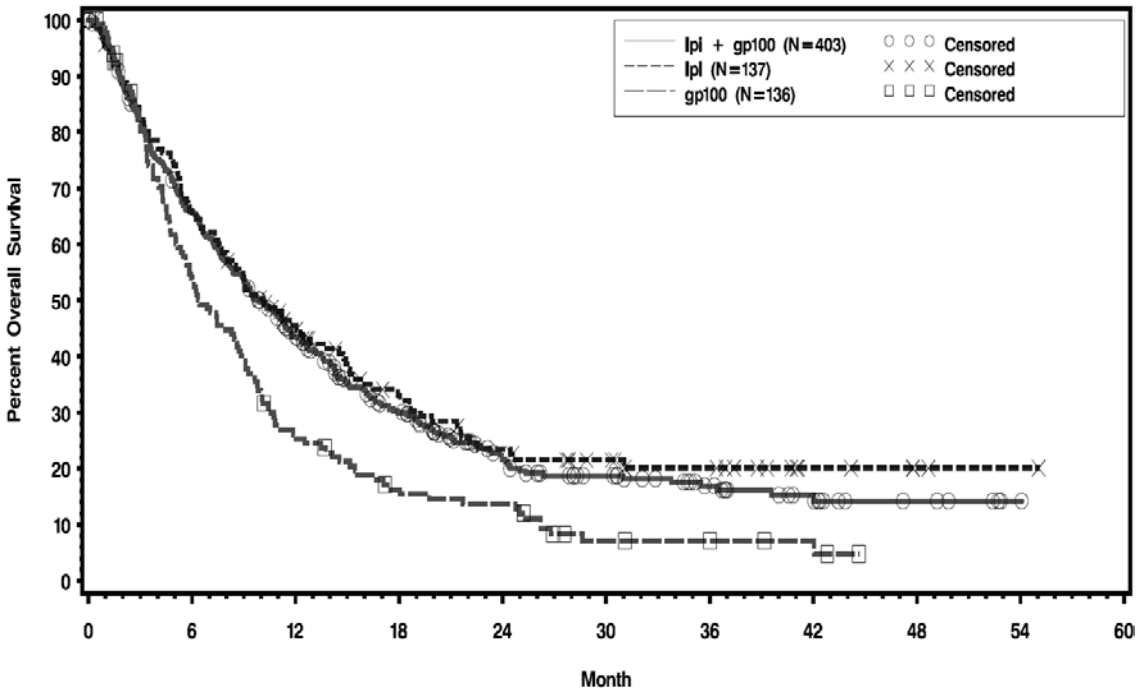
The OS results are shown in Table 5 and Figure 2.

Table 5: MDX010-20 Overall Survival Results

	Ipilimumab n = 137	Ipilimumab + gp100 n = 403	gp100 n = 136
Hazard Ratio (vs gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p = 0.0026[a]	p = 0.0004	
Hazard Ratio (vs ipilimumab) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

[a]Not adjusted for multiple comparisons.

Figure 2: MDX010-20 - Overall Survival by Treatment (ITT Population)



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the ipilimumab + gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the ipilimumab arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the ipilimumab + gp100 arm and has not been reached in the ipilimumab or gp100 arm.

1.4.5.3 CA184024 (Phase 3, previously untreated melanoma, 10 mg/kg)

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg/kg or placebo cycles 1-4, and as maintenance after completion of chemotherapy.

The two arms were well balanced regarding most baseline characteristics, as shown in Table 6.

Table 6: CA184024 Baseline Characteristics

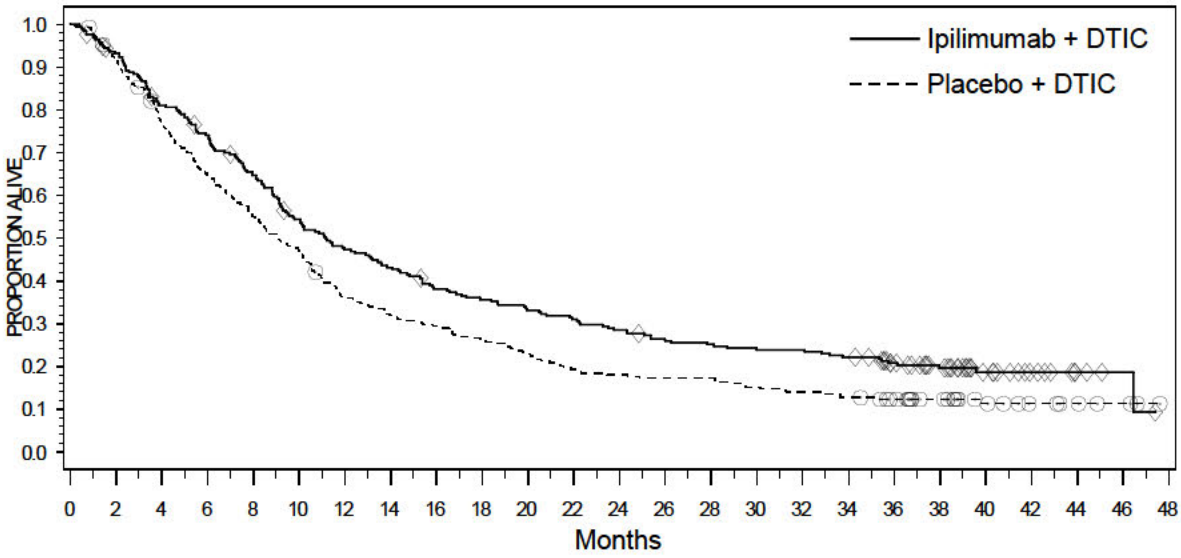
	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Age (years)		
Mean	57.5	56.4
Gender (%)		
Male	60.8	59.1
Female	39.2	40.9
M Stage (%)		
M0	2.4	3.2
M1a	14.8	17.1
M1b	25.6	24.6
M1c	57.2	55.2
ECOG PS (%)		
0	70.8	71.0
1	29.2	29.0
LDH (%)		
≤ ULN	62.8	55.6
> ULN	37.2	43.7
≤ 2x ULN	86.4	85.3
> 2x ULN	13.6	13.9
Prior adjuvant therapy (%)	26.4	26.6
Prior therapy for advanced disease (%)	0	0

Patients on the ipilimumab arm received a median of 3 ipilimumab induction doses, versus 4 placebo induction doses on the placebo arm. A total of 17.4% and 21.1% of patients continued to receive maintenance ipilimumab or

placebo, for a median of 4 and 2 doses, respectively. The number of patients who received all 8 dacarbazine doses was 12.2% in the ipilimumab arm, and 21.5% in the placebo arm.

The study met its primary end-point of prolonging overall survival in patients treated with ipilimumab (HR 0.72 (95% CI, 0.59 – 0.87), median OS 11.2 vs 9.1 months, p = 0.0009). The OS Kaplan-Meier curve is presented in Figure 3.

Figure 3: CA184024 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects



One, two and three year survival rates were 47.3%, 28.5% and 20.8% in the ipilimumab arm, and 36.3%, 17.9% and 12.2% in the placebo arm.

PFS, a secondary end-point, was also prolonged by the addition ipilimumab, HR 0.76 (95% CI, 0.63 - 0.93). The median PFS was 2.8 months in the ipilimumab and vs 2.6 months in the placebo arm, p = 0.006.

BORR was increased from 10.3% in the placebo arm to 15.2% in the ipilimumab arm (Table 7). More importantly, duration of response was more than twice as long in the ipilimumab arm (19.3 months) than in the placebo arm (8.1 months).

Table 7: CA184024 Tumor Response		
	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

1.4.5.4 10 mg/kg Dosing with Ipilimumab

In melanoma, Phase 3 studies show improved survival at both 3 mg/kg (study MDX010-20) as well as with 10 mg/kg (study CA184024). Several additional conducted trials studied the efficacy and safety of 10 mg/kg dosing, and additional information gained from these trials is listed below:

- A dose of 10 mg/kg is necessary to ensure a blockade of the CTLA-4 pathway: *in vitro* a concentration of 20 μg/mL of ipilimumab was the minimal concentration able to fully abrogate the binding of CTLA-4 to B7.1 and B7.2. With a dose of 3 mg/kg q3w 30% achieved a trough concentration of ipilimumab greater than 20 μg/mL, compared to 95% of subjects treated at 10 mg/kg q3w.
- In addition, in all ipilimumab trials examined to date, mean Absolute Lymphocyte Count (ALC) increased after ipilimumab treatment throughout the 12-week induction-dosing period, in a dose-dependent manner. In an analysis of ipilimumab at 0.3, 3, or 10 mg/kg in melanoma studies CA184007, CA184008, and CA184022 combined, the rate of change in ALC after ipilimumab treatment was significantly associated with dose ($p = 0.0003$), with the largest rate at 10 mg/kg ipilimumab. Moreover, the rate of change in ALC over the first half of the induction-dosing period was significantly associated with clinical activity in these studies ($p = 0.009$), where clinical activity was defined as CR, PR, or prolonged SD (ie, SD lasting at least 6 months from first dose). Although these analyses alone could not determine whether the rate of change in ALC was specifically associated with clinical activity in response to ipilimumab treatment, as opposed to being generally prognostic, these results do suggest a potential benefit to higher rates of ALC increase after

ipilimumab treatment. Among the 3 doses evaluated, 10 mg/kg ipilimumab led to the greatest such rates.

- In the 3 primary studies conducted in advanced melanoma (CA184007, CA184008, and CA184022), subjects treated with 10 mg/kg during the induction period had the highest response, disease control rates, median OS as well as 1-year and 2-year survival rates compared to other doses. The CA184022 data are summarized in Table 8.

Table 8: Summary of Phase 2 Response Data in Melanoma (CA184022)

	10 mg/kg (n = 72)	**3 mg/kg (n = 72)**	**0.3 mg/kg (n = 73)**
BORR (mWHO) – % (95% CI)	11.1 (4.9 - 20.7)	4.2 (0.9 - 11.7)	0 (0.0 - 4.9)
DCR (mWHO) – % (95% CI)	29.2 (19.0 - 41.1)	26.4 (16.7 - 38.1)	13.7 (6.8 - 23.8)
Survival rate at 1 year - % %, 95% CI	48.64 (36.84, 60.36)	39.32 (27.97, 50.87)	39.58 (28.20, 51.19)
Survival rate at 2 year - % %, 95% CI	29.81 (19.13, 41.14)	24.20 (14.42, 34.75)	18.43 (9.62, 28.22)
Overall median survival 95%CI (months)	11.43 (6.90, 16.10)	8.74 (6.87, 12.12)	8.57 (7.69, 12.71)

Finally, the dose and schedule in study CA184156 is the one that was evaluated in the signal finding study CA184041, with an acceptable safety profile and improvement of irPFS and OS.

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma.

1.4.5.5 Advanced Melanoma

Ipilimumab prolonged survival in subjects with pre-treated advanced melanoma are based on results from MDX010-20 (Phase 3) supported by data from Phase 2 studies; the primary efficacy and safety studies are summarized in Table 9. The primary endpoint in MDX010-20 was OS, which was also a key secondary endpoint in Phase 2 studies.

Table 9: Studies Supporting the Efficacy and Safety of Ipilimumab in Subjects with Advanced Melanoma						
				# Randomized or Enrolled/Treated		
Study No. (Phase)	Populations	Primary Efficacy Endpoint	Doses Studies	3 mg/kg	10 mg/kg	Total
MDX010-20 (Phase 3)	HLA-A2*0201-positive, previously treated, unresectable Stage III or IV melanoma	OS	3 mg/kg q3 wk x 4 ± gp100 (induction) followed by re-induction	540/512	--/--	676/643[a]
CA184022 (Phase 2)	Previously treated, unresectable Stage III or IV melanoma	BORR	0.3, 3, or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	72/71	72/71	217/214
CA184004 (Phase 2) Biomarker Study	Unresectable Stage III or IV melanoma	BORR	3 or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	40/40	42/42	82/82
CA184008 (Phase 2)	Previously treated unresectable State III or IV melanoma	BORR	10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	--/--	155/155	155/155
CA184007	Unresectable Stage III or IV melanoma	BORR	10 mg/kg q3 wk x 4 ± budesonide (induction) followed by maintenance dosing q12 wk	--/--	115/115	115/115
Additional Studies						
MDX010-08(Phase 2)	Chemotherapy-naive advanced melanoma	ORR	3 mg/kg q4 wk x 4 ± DTIC (induction)	78/74	--/--	78/74
CA184042 (Phase 2)	Stage IV melanoma with brain metastases	DCR	10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	--/--	28/28[b]	28/28[b]
MDX010-28 (Phase 2) Survival Follow-up Study	Subjects enrolled in earlier Medarex studies, including MDX010-08 and MDX010-15[c]	OS	N/A	--/N/A	--/NA	--/N/A

BORR = best overall response rate; DCR = disease control rate; DTIC = dacarbazine; N/A = not applicable; ORR = overall response rate; OS = overall survival; PK = pharmacokinetics.

[a] Total includes 136 randomized/131 treated subjects in the gp100 treatment group.

[b] Information is presented only for subjects enrolled in MDX010-20, Arm A.

[c] MDX010-15 was primarily a PK study that evaluated ipilimumab at single and multiple doses.

Source: Reference 16-23

1.5 Bevacizumab CLINICAL Experience

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. The following discussion

summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3months; p< 0.001). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; p< 0.001), overall response rate (35% vs. 45%; p< 0.01) and duration of response (7.1vs. 10.4 months; p< 0.01) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5 FU-based chemotherapy for subjects with metastatic colorectal cancer.

Pharmacokinetic data with 5 mg/kg every 2 weeks shows comparability with 7.5 mg every three weeks and 10 mg/kg every 2 weeks is comparable to 15 mg/kg every 3 weeks.

1.5.1 Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF), gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: Hypertension has been commonly seen in bevacizumab clinical trials to date and oral medications have been used to manage the hypertension when indicated. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS)[21, 22]. RPLS may include signs and symptoms of headache, altered mental function, seizures, and visual disturbances / cortical blindness and requires treatment, which should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

Proteinuria: Proteinuria has been commonly seen in bevacizumab clinical trials to date. The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1 or 2. In study AVF2107g, none of the 118 patients

receiving bolus-IFL plus placebo, three of 158 patients (2%) receiving bolus-IFL plus bevacizumab, and two of 50 (4%) patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (> 3.5 g protein/24 hr). Rare events of nephrotic syndrome have occurred, and bevacizumab should be discontinued in patients with nephrotic syndrome.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of **venous TE** events that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of **arterial TE** events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina**.** A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively) (Skillings et al., 2005). Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. See the bevacizumab Investigator Brochure for additional information on risk factors.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised

when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, and breast) and may be higher in incidence in some tumor types.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone[23]. Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 20 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage was observed in phase I and phase II bevacizumab studies. Six serious events, of which 4 had fatal outcome, were observed in a phase II trial of patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive hemoptysis in patients with either squamous cell histology and/or tumors located in the center of the chest in close proximity to major blood vessels. In five of these cases, these hemorrhages were preceded by cavitation and/or necrosis of the tumor. Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Congestive heart failure: CHF has been reported in bevacizumab clinical trials and may be increased in incidence in patients with prior exposure to anthracyclines or prior irradiation to the chest wall. In a

phase III trial (AVF2119g) of capecitabine with or without bevacizumab for metastatic breast cancer, 7 subjects (3.1%) who received capecitabine plus bevacizumab developed clinically significant CHF compared with 2 subjects (0.9%) treated with capecitabine alone; of note, all subjects in this trial had had prior anthracycline treatment. In addition, 2 subjects had a left ventricular ejection fraction < 50% at baseline and 2 others had prior left chest wall irradiation. A recently published phase II study in subjects with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or decreases to < 40% in left ventricular ejection fraction) of 48 subjects treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but one of these subjects had significant prior exposure to anthracyclines as well[24]. Other studies are ongoing in this patient population. Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

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

1.6 Overall Risk/Benefit Assessment

Ipilimumab is the first drug to demonstrate prolonged survival in subjects with pre-treated advanced melanoma, based on a large, multinational, double-blind, pivotal, Phase 3 study supported by a comprehensive Phase 2 program.

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab impacts tumor cells indirectly, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in subjects who are not experiencing rapid clinical deterioration, confirmation of progression is recommended, at the investigator's discretion, to better understand the prognosis as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefitting from treatment. Immune-related (ir) response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response, and in some instances is associated with slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses. Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its improvement in OS.

The immune-based mechanism of action is also reflected in the safety profile. The most common drug-related AEs are immune-mediated, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. As previously discussed, the immune-mediated adverse reactions primarily involve the GI tract, skin, liver, endocrine glands, and nervous system.

The early diagnosis of immune-mediated adverse reactions is important to initiate therapy and minimize complications. Immune-mediated adverse reactions are generally manageable using symptomatic or immunosuppressive therapy as recommended through detailed diagnosis and management guidelines, as described fully in the current IB. The management guidelines for general immune-mediated adverse reactions and ipilimumab-related GI toxicities, hepatotoxicity, endocrinopathy, and neuropathy are provided in the appendices of the current IB.

In summary, ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with pre-treated advanced melanoma and evidence of clinical activity in randomized studies in other tumor types. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-mediated toxicities, suggest an acceptable benefit to risk ratio.

Ipilimumab has been shown to prolong survival in patients with metastatic melanoma. Means to improve upon this foundation of clinical benefit for patients are worthy of pursuit. Experience thus far suggests that the combination of bevacizumab plus ipilimumab can result in enhanced immune activation with clinical benefits for patients. The adverse events have been easily managed. Given our preliminary data so far including clinical outcomes, immune activation, and pathologic evaluations of post-treatment biopsies, the ability to make an adequate assessment of clinical activity and effects on immune function to the combination of ipilimumab plus bevacizumab versus ipilimumab alone would best be performed in a randomized fashion.

The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options.

1.7 Study Rationale

To better define the potential benefit of adding bevacizumab to ipilimumab in patients with metastatic melanoma, this is best performed in a prospective randomized manner. In the current trial, patients will be randomized to ipilimumab 3 mg/kg every 3 weeks x 4 with maintenance every 12 weeks versus ipilimumab 3 mg/kg plus bevacizumab 15 mg/kg every 3 weeks x 4, continued with every three week bevacizumab and every 12 week ipilimumab maintenance. Patients will be previously untreated for unresectable stage III or stage IV disease or are permitted to have received up to one prior therapy.

2. Objectives

2.1 Primary Endpoint

To compare overall survival for patients receiving ipilimumab plus bevacizumab versus ipilimumab alone.

2.2 Secondary Objectives

2.2.1 To evaluate the progression free survival, response rate and safety in patients receiving ipilimumab plus bevacizumab versus ipilimumab alone.

2.2.2 To evaluate the utility of immune related response criteria (irRC) in patients receiving ipilimumab plus bevacizumab versus ipilimumab alone.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years

_____ 3.1.2 ECOG Performance status: 0 or 1

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_____ 3.1.3 Untreated or previously received one treatment regimen for measurable unresectable Stage III or Stage IV melanoma (AJCC 2010) (for BRAF wild-type, and regardless of HLA type). Untreated or previously received up to two treatment regimens for measurable unresectable Stage III or Stage IV melanoma (AJCC 2010) (for BRAF mutant, and regardless of HLA type; If 2 prior regimens, one should be a BRAF inhibitor). This does not include any therapies given in the adjuvant setting.

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_____ 3.1.4 Prior treatment (chemo, radiation, hormone, and immune therapies) must be completed > 4 weeks prior to randomization (> 6 weeks prior to randomization for nitrosoureas, mitomycin C, and checkpoint inhibitors).

_____ 3.1.5 Patients who received prior therapy with anthracylines should have a baseline MUGA or echo with a normal ejection fraction within 28 days prior to randomization.

_____ 3.1.6 Patients must have recovered from any acute toxicity associated with prior therapy by the start of study treatment.

_____ 3.1.7 Women must not be pregnant or breast-feeding due to the unknown effects on the fetus or infant.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.8 All sites of disease must be evaluated within 4 weeks prior to randomization. Patients must have measurable disease as defined in Section 6.

_____ 3.1.9 Patients must have the following required values for initial laboratory tests obtained within 4 weeks prior to randomization (ULN: institutional upper limit of normal):

- WBC ≥ 2000/uL
- ANC ≥ 1000/uL
- Platelets ≥ 75 x 10^3/uL
- Hemoglobin ≥ 9 g/dL
- Creatinine ≤ 2.0 x ULN
- AST/ALT ≤ 2.5 x ULN for patients without liver metastases and ≤ 5 x ULN for patients with liver metastases
- Serum Bilirubin ≤ 2.0 x ULN (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)

Rev. 8/14 _____3.1.10 Patients BRAF mutation status must be known.

_____3.1.11 No Concomitant therapy with any of the following: IL 2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids; must have been discontinued ≥ 4 weeks prior to randomization.

_____3.1.12 No infection with HIV. Due to the mechanism of action of ipilimumab and bevacizumab, activity and side effects in an immune compromised patient are unknown.

_____ 3.1.13 No active infection with Hepatitis B.

_____3.1.14 No active or chronic infection with Hepatitis C.

_____ 3.1.15 Patients are ineligible if they have any history of CNS metastases.

_____3.1.16 Patients are ineligible if they have a history of any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix.

_____ 3.1.17 Patients are ineligible if they have a history of autoimmune disease, as follows: Patients with a history of inflammatory bowel disease are

excluded from this study as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]). Patients with motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis) are excluded. Patients with a history of autoimmune thyroiditis are eligible if their current thyroid disorder is treated and stable with replacement or other medical therapy.

_____ 3.1.18 Patients are ineligible if they have an active infection.

_____ 3.1.19 Patients are ineligible if they have a history of prior treatment with ipilimumab, bevacizumab, or prior CD137 agonist or CTLA-4 inhibitor or agonist. Patients may be treatment naïve or have had one prior systemic therapy for metastatic disease as outlined in the eligibility criteria. Patients may have received prior anti-PD-1 or anti-PD-L1 as per current protocol eligibility, although they are not currently commercially approved in the front line setting.

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_____ 3.1.20 Patients are ineligible if they have a history of any underlying medical or psychiatric conditions or require any medications or treatment that in the opinion of the principal investigator may interfere with compliance, make the administration of study drug hazardous or obscure the interpretation of adverse events, such as a condition associated with frequent diarrhea.

_____ 3.1.21 Patients are ineligible if they have any concurrent medical condition requiring the use of systemic steroids. (Use of inhaled or topical steroids is acceptable).

_____ 3.1.22 Patients are ineligible if they have inadequately controlled hypertension (defined as systolic blood pressure > 150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).

_____ 3.1.23 Patients are excluded if they have any prior history of hypertensive crisis or hypertensive encephalopathy.

_____ 3.1.24 Patients are excluded if they have New York Heart Association (NYHA) Grade II or greater congestive heart failure.

_____ 3.1.25 Patients are excluded if they have a history of myocardial infarction or unstable angina within 6 months prior to randomization.

_____ 3.1.26 Patients are excluded if they have a history of stroke or transient ischemic attack within 6 months prior to randomization.

_____ 3.1.27 Patients are excluded if they have known significant vascular disease (e.g., aortic aneurysm, aortic dissection).

_____ 3.1.28 Patients are excluded if they have symptomatic peripheral vascular disease.

_____ 3.1.29 Patients are excluded if they have evidence of bleeding diathesis or coagulopathy.

_____ 3.1.30 Patients are excluded if they have had a surgical procedure or a significant traumatic injury within 28 days prior to randomization.

_____ 3.1.31 Patients are excluded if they have had a biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to randomization.

_____ 3.1.32 Patients are excluded if they have history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization.

_____ 3.1.33 Patients are excluded if they have a non-healing wound or ulcer.

_____ 3.1.34 Patients are excluded if they have proteinuria at screening as demonstrated by either:

- Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible) **OR**
- Urine protein: creatinine (UPC) ratio ≥ 1.0 at screening. For UPC ratio > 1, a 24-hour urine protein should be obtained and the level should be <1000mg.

  NOTE: Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. UPC ratio of spot urine is an estimation of the 24 hour urine protein excretion. A UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

  [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL

  [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

_____ 3.1.35 Patients must not have known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

_____ 3.1.36 Patients are excluded if they have a history of hemoptysis (bright red blood of 1/2 teaspoon or more per episode) within 3 months prior to randomization.

_____ 3.1.37 Patients are excluded if they have current, ongoing treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin). Subjects should have not taken full-dose warfarin or equivalent for at least 2 weeks prior to randomization.

_____ 3.1.38 Patients are excluded if they have current or recent (within 10 days of enrollment) use of aspirin (> 325 mg/day) or chronic use of other NSAIDs.

_____ 3.1.39 Patients are excluded if they use medications that inhibit platelet function (e.g., dipryidamolde, epoprostenol, epitfibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and ibuprofen and related compounds) unless subject has been off treatment for at least 2 weeks prior to randomization.

_____ 3.1.40 Patients are excluded if they have known involvement of melanoma within the gastrointestinal tract.

_____ 3.1.41 Patients are excluded for any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).

_____ 3.1.42 Women of childbearing potential and sexually active males must agree to practice abstinence or use an accepted and effective method of contraception.

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster

affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

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Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study..

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E3612** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E3612**
- Click on the Site Registration Documents link

Requirements for E3612 site registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal

EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

FAX: 215-569-0206

MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed

consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment:

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN

can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

- Institution and affiliate name (Institution CTEP ID)
- Investigator's name (NCI number)

4.3 Patient Identification

- Patient's initials(first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.5 Stratification Factors

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- Prior systemic therapy for unresectable stage III or IV melanoma (no vs. yes)
- BRAF mutation status (wild type vs. mutation)

4.6 Additional Requirements

4.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.6.2 Pathological samples are required to be submitted for central diagnostic review (mandatory) and for future undefined research (per patient consent) as indicated in Section 10.

4.6.3 Biological samples are to be submitted for future undefined research as outlined in Section 10.

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4.6.4 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E3612 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

Patients will be randomized to either Arm A or Arm B.

Patients must receive their first induction dose within seven working days of randomization.

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The total dose must be calculated using the most recent subject actual weight (obtained within 3 days of the dosing visit, and prior to the infusion). The dose will not be recalculated unless the patient has ±10% weight change for both agents.

5.1.1 Arm A

Induction Therapy: Cycles 1-4

Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4

Maintenance Therapy: Cycles 5 and higher

Ipilimumab 3 mg/kg IV Day 1 of every 4th cycle (12 weeks) starting Cycle 8*

***Maintenance until excessive toxicity, progression or determination that treatment is no longer clinically beneficial.**

Cycle=21 days

5.1.2 Arm B

Induction Therapy: Cycles 1-4

Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4

plus

Bevacizumab 15 mg/kg IV Day 1 Cycles 1-4

Maintenance Therapy: Cycles 5 and higher

Ipilimumab 3 mg/kg IV Day 1 of every 4th cycle (12 weeks) starting Cycle 8*

plus

Bevacizumab 15 mg/kg IV Day 1 of each cycle starting Cycle 5*

*** Maintenance until excessive toxicity, progression or determination that treatment is no longer clinically beneficial.**

Patients will receive ipilimumab first followed by bevacizumab. There is no planned delay between the ipilimumab and bevacizumab administration. If it is found that pre-medication is necessary prior to bevacizumab administration, then a delay is allowed.

Cycle=21 days

5.1.3 Ipilimumab Dose Calculation

Each patient will receive ipilimumab 3 mg/kg IV over 90 minutes every 21 days x 4, followed by 3 mg/kg IV over 90 minutes every 12 weeks during maintenance.

Ipilimumab infusions should be given over 90 minutes (not bolus or IV push).

Calculate **Total Dose** as follows:

Patient body weight in kg x 3 mg/kg = total dose in mg

Calculate **Ipilimumab Infusion Volume** as follows:

Total dose in mg ÷ 5 mg/mL = ipilimumab volume in mL

Ipilimumab should be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL.

Calculate **Total Infusion Volume and Rate of Infusion** as follows:

Total infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min.

For example, a patient weighing 114 kg (250 lb) would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 69 mL (342 mg ÷ 5 mg/mL = 69 mL) + 273 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP at a rate of approximately 3.8 mL/min (342 mL ÷ 90 minutes) over 90 minutes.

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5.1.4 Bevacizumab Dose Calculation

Each patient in Arm B will receive bevacizumab 15 mg/kg IV over 90 minutes (first dose). Subsequent doses may be administered over 60 minutes if tolerated. If tolerated at 60 minutes, may administer over 30 minutes. Bevacizumab will be given following ipilimumab every 21 days (3 weeks) throughout induction and maintenance phases.

Bevacizumab infusions should not be given bolus or IV push. Pre-medications may be given prior to bevacizumab according to institutional standards.

Calculate **Total Dose** as follows:

Patient body weight in kg x 15 mg/kg = total dose in mg

Calculate **Bevacizumab Infusion Volume** as follows:

Total dose in mg ÷ 25 mg/mL = bevacizumab volume in mL

Bevacizumab should be diluted in a 100 mL 0.9% Sodium Chloride Injection, USP.

Calculate Rate of Infusion as follows:

Total infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min (first dose).

Total infusion volume in mL ÷ 60 minutes = rate of infusion in mL/min (second dose).

Total infusion volume in mL ÷ 30 minutes = rate of infusion in mL/min (subsequent doses).

For example, a patient weighing 114 kg (250 lb) would be administered 1710 mg bevacizumab (114 kg x 15 mg/kg = 1710 mg) with an infusion volume of 68.4 mL (1710 mg ÷ 25 mg/mL = 68.4 mL) + 31.6 mL 0.9% Sodium Chloride Injection, USP at a rate of approximately 1.1 mL/min over 90 minutes or 1.7 mL/min over 60 minutes or 3.3 mL/min over 30 minutes.

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5.2 Adverse Event Reporting Requirements

NOTE: Effective April 1, 2018 all expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines for this study will continue to be based on CTCAE version 4.0 terminology and grading.

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timely monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

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- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event. If the protocol uses multiple investigational agents and has an AE listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) and
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

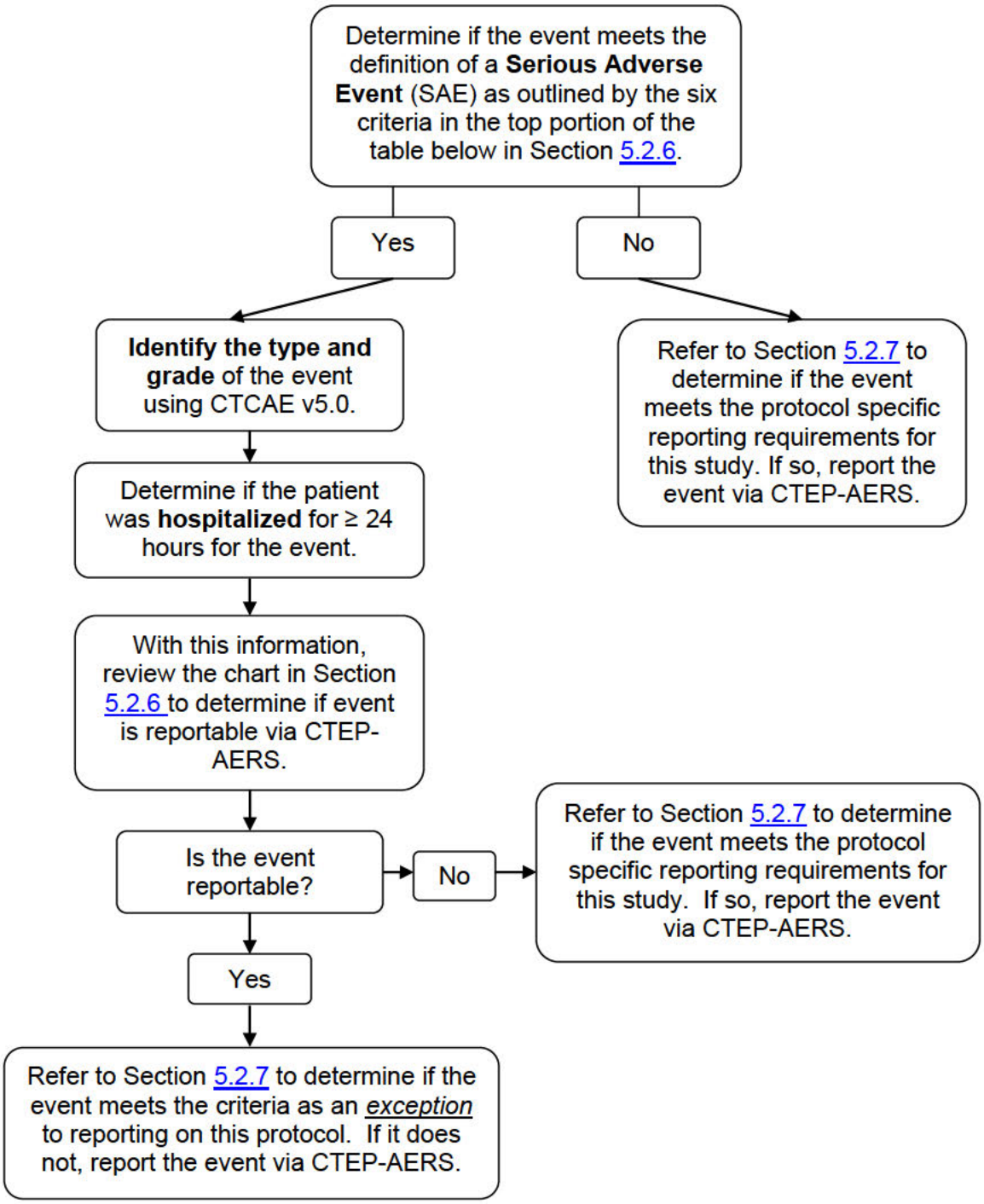
- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E3612 and outline the specific expedited adverse event reporting requirements for study E3612.

Rev. Add8

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

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

5.2.6 Expedited Reporting Requirements for Arms A and B on protocol E3612

Investigational Agents: Ipilimumab and Bevacizumab

Commercial Agents: None

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

5.2.7 Additional instructions, requirements and exceptions for protocol E3612

Additional Instructions:

Rev. Add8

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at 301-897-7497 or aemd@tech-res.com. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study:** A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

E3612 specific expedited reporting requirements:

- **Pregnancy:**

  Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Ipilimumab or Bevacizumab, or within 28 days of the subject's last dose of Ipilimumab or Bevacizumab, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.
- **Immune Related Adverse Events (IRAEs)**: Any grade 3 or higher immune related adverse events (see Section 5.4.1.5 for definitions) must be reported via CTEP-AERS within 10 calendar days of learning of the event, regardless of whether hospitalization is required. If available, please submit any supporting data as well (ie: autoimmune serology tests or biopsy reports).

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  NOTE: In order to appropriately report these events to regulatory agencies, please be sure to state that the event being reported is an IRAE in the 'Description of Event' section of the CTEP-AERS report.

- **Vasculitis**: Any grade 3 or higher vasculitis must be reported via CTEP-AERS within 10 calendar days of learning of the event, regardless of whether hospitalization is required.
- **Bowel Perforation**: Any grade 3 or higher bowel perforation must be reported via CTEP-AERS within 10 calendar days of learning of the event, regardless of whether hospitalization is required.

E3612 specific expedited reporting exceptions:

The adverse events listed below **do not** require expedited reporting via CTEP-AERS:

If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

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NOTE: Since Arm B is a combination protocol arm using multiple investigational agents, if the AE being reported appears on both the Ipilimumab AND Bevacizumab SPEERs, use the lower of the grades to determine if expedited reporting is required.

5.2.8 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Reporting Second Primary Cancers

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.

2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require <u>*both routine and expedited reporting*</u> as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Rev.3/16
Rev. 2/17

5.3.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER

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NOTE: Since Arm B is a combination protocol arm using multiple investigational agents, if the AE being reported appears on both the Ipilimumab AND Bevacizumab SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

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

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune

hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

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

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

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. 8/14

5.3.2 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

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

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NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

NOTE: Since Arm B is a combination protocol arm using multiple investigational agents, if the AE being reported appears on both the Ipilimumab AND Bevacizumab SPEERs, use the lower of the grades to determine if expedited reporting is required.

Rev. 11/16
Rev. Add9

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***
		Chest pain - cardiac[3]	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura

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

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

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

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

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

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

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

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

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

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

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb

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

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

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

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

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

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

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

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

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

5.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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 website (http://ctep.cancer.gov).

5.4.1 Ipilimumab Dose Modification and Toxicity Management

5.4.1.1 Dose and Schedule Modifications for Ipilimumab

Patients may develop study drug-related toxicities that may require dose delay, skipping doses or dose discontinuation. Treatment modifications will be made based on specified safety criteria. Patients will delay, skip or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be definitely, probably, or possibly related to ipilimumab treatment. There will be no dose reductions. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab.

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NOTE: During induction, if ipilimumab is held, bevacizumab should also be held to maintain concurrent administration.

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5.4.1.1.1 Criteria to delay one dose of ipilimumab

Delay ipilimumab dosing for the following treatment related adverse events:

- Any > Grade 2 non-skin related adverse event (including Immune-Related Adverse Events (IRAEs), except for laboratory abnormalities.

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- Any ≥ Grade 3 skin related adverse events regardless of causality (including Immune-Related Adverse Events (IRAEs). Resolution to grade 1 or better required before continuing treatment.
- Further with regards to skin rashes, all study drugs should be held as well as any other agents possibly associated with toxic epidermal necrolysis (TEN) or Stevens-Johnson Syndrome (SJS) until an evaluation has been done. This would include any patient with possible erythema multiforme (EM) or SJS and for any grade 2 purpuric or bullous rash.
- Any ≥ 2 laboratory abnormality believed to be related to study treatment.

- All study drugs should be held for suspected colitis until an appropriate evaluation has been completed. Please refer to Appendix VIII for GI Toxicity Management Algorithm.
- Patients who develop hypophysitis may continue treatment once they are on a stable replacement regimen. Please refer to Appendix XII Neurological Toxicity Management Algorithm.
- Patients with hepatitis may continue once their liver function tests resolve to pretreatment grade. Please refer to Appendix IX Hepatotoxicity Management Algorithm for management recommendations.

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5.4.1.1.2 Criteria to resume ipilimumab treatment

Restarting ipilimumab applies only to grade 2 events and some grade 3 events as excepted (skin rash, aseptic meningitis, encephalitis, and thryroiditis). Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 3 weeks of initial dose administration:

- If the adverse event has resolved, restart ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (3 weeks [+/- 3 days] during first 4 cycles and 12 weeks [+/- 1 week] during maintenance phase), the next scheduled dose will be omitted.
- If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the primary investigator (or co-primary investigator, if the PI is not available) prior to implementation.
- Drug may be restarted following any grade 2 or greater immune-related adverse event after complete resolution of ≤ Grade 1 severity or returns to baseline.
- Patients with hepatitis, pancreatitis, pneumonitis, and colitis are at risk for exacerbation and should resolve to

Grade 0 or grade at baseline before retreatment.

5.4.1.2 Criteria for permanent discontinuation of ipilimumab

5.4.1.2.1 Permanent Discontinuation for Related Adverse Events

Ipilimumab administration must be permanently discontinued if any of the following Related Adverse Events occurs:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other ≥ Grade 3 non-skin related adverse event with the exception of events listed in Section 5.4.1.2.3.
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- Grade 3 uveitis

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- For all grade 3 or greater immune-related adverse events, the patient should be taken off treatment with the exception listed in Section 5.4.1.2.3.

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- All patients treated with steroids for grade ≥ 3 events should have ipilimumab discontinued. All patients treated with steroids for grade ≥ 2 events should have ipilimumab held until resolution to ≤ Grade 1 for at least 2 weeks following removal of steroid treatment.

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- New immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and should require permanent discontinuation of ipilimumab.

5.4.1.2.2 Skipped Dose Maximum

A maximum of 1 missed scheduled dose is allowed. If more than 1 dose is missed, patient must discontinue study treatment.

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5.4.1.2.3 Exceptions to permanent discontinuation of ipilimumab

Ipilimumab administration may be resumed in the following cases:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy.
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. Note: Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.
  - Patients with thyroiditis hypophysitis who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses only of corticosteroids.

5.4.1.3 Treatment of Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab

will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritis, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

For mild symptoms (e.g., localized cutaneous reactions such as mild pruritis, flushing, rash):

- Decrease the rate of infusion by half until recovery from symptoms, remain at bedside and monitor patient.
- Complete the ipilimumab infusion at the initial planned rate.
- Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
- Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.

For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritis, flushing, rash, dyspnea, hypotension with systolic BP < 80 mmHg):

- Interrupt ipilimumab.
- Administer diphenhydramine 50 mg IV.
- Monitor patient closely until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.

Resume ipilimumab infusion after recovery of symptoms. At the discretion of the treating physician, ipilimumab infusion may be resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate.

- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema):

- Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with methylprednisolone 100 mg IV, as needed.
- Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
- No further ipilimumab will be administered.

In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritis), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.4.1.4 Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.4.1.5 Immune-Related Adverse Events (IRAE's)

5.4.1.5.1 Definition of Immune-Related Adverse Events (IRAE's)

Blocking CTLA 4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were noted in previous ipilimumab studies. These drug-related events are presumptive immune-related adverse events, now termed IRAEs.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology

associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE form.

5.4.1.5.2 Monitoring and Treatment of Immune-Related Adverse Events (IRAE's)

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment.

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5.4.1.6 Management/Next Dose for Ipilimumab Cardiac Toxicities

Cardiac*	Management/Next Dose for Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥ 2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥ 2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (Consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	
• Drug will be held for grade 2 cardiac dysfunction pending evaluation • Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur • Treatment with steroids as clinically indicated	

5.4.2 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: 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. 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.

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Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 2.

5.4.2.1 Bevacizumab Dose Modifications Due to Adverse Events

Table 2: Bevacizumab Dose Management Due to Adverse Events

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

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Version 4 Grade**	**Action to be Taken**
Allergic reactions Or **Infusion-related reactions** Or **Anaphylaxis**	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. • Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial), arterial ischemia	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
- Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - Any peripheral or visceral arterial ischemia/ thrombosis	Grade 3-4	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Version 4 Grade**	**Action to be Taken**
Thromboembolic Event (Venous)	[Note: Patients with primary lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** all of the criteria below are met: - The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study - The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg) • Grade 3 (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg)	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg* • For hypertension that is refractory requiring delay of bevacizumab for > 4 weeks, discontinue bevacizumab
	Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE Version 4 Grade**	**Action to be Taken**
Heart Failure OR **Left Ventricular (LV) dysfunction**	• Heart failure ≥ Grade 2 • LV dysfunction ≥ Grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis dipstick. If Dipstick ≥ 2+ proteinuria, 24-hour urine protein should be obtained	Dipstick ≥ 2+	Hold bevacizumab and obtain 24 hour urine protein
	If 24-h urine protein < 2g	Continue bevacizumab
	If 24-h urine protein ≥ 2g	• Hold bevacizumab until 24-hour urine protein < 2.0 g • Discontinue bevacizumab if urine protein does not recover to < 2.0 g after 8 weeks of bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (not CNS or pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab

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

NOTE: If bevacizumab is to be discontinued due to adverse effects determined related to bevacizumab, ipilimumab may be continued if at the discretion of the treating physician it is felt that it can be safely done so knowing the possible side effect profile of ipilimumab. This may be done if the side effects of bevacizumab have resolved to ≤ grade 1 and all other treatment parameters have been met.

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

5.5 Prohibited and Restricted Therapies During the Study

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen

(including those for common medical conditions) for up to one month pre and post dosing with ipilimumab. Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab and/or bevacizumab treatments.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
- CD137 agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- Physiologic replacement doses of corticosteroids are permitted if required
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug)

5.6 Supportive Care

5.6.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.6.2 Please refer to Appendices V-VII for algorithms pertaining to immune related adverse events.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the schedule in the E3612 Forms Completion Guidelines.
- Patient withdraws consent.
- Excessive or unexpected toxicity (see Section 5.4), pregnancy, change in medical condition or noncompliance with the study protocol that in the opinion of the investigator, necessitates removal of patient from treatment.
- Progression of disease after 12 weeks of treatment: Patients who progress clinically at or before the 12th week of treatment will discontinue protocol therapy if other therapy (surgery, radiation, chemotherapy) is needed urgently. However, patients who experience progression of disease that does not require urgent change in therapy are eligible to receive 24 weeks of treatment. See Section 6.1.6.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect-Solid Tumors-RECIST

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

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

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

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be

≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the

sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

6.1.3 Methods for Evaluation of Disease

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

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must

be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

Tumor Markers

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

Cytology, Histology

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

FDG-PET

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is generally a sign of PD based on a new lesion. However, immunotherapeutic agents such as ipilimumab as known to generate a systemic immune response leading to enhanced immune cellular infiltration or tumor or lymph nodes. Therefore, a positive FDG-PET lesion at follow-up needs to be carefully assessed to ensure accurate response assessment and a biopsy should be pursued if in doubt.

   No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is generally a sign of PD, but care must be taken in assessing the tumor response, as noted in the prior paragraph. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

b. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. To be assigned a status of complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. To be assigned a status of partial response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.3.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease).

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesions.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease

progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 12 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

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

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

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

6.1.4.5 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

6.1.4.6 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.1.4.7 Definition of Tumor Response Using irRC

NOTE: This section is for secondary endpoint assessment.

The sum of the products of the two largest diameters of lesions (SPD) at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

6.1.4.7.1 Definition of Target Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all target lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all target and all new measurable lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by $\geq$ 25% when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking SPD of all target lesions and any new lesions) when compared to SPD at nadir.

6.1.4.7.2 Definition of Non-Target Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all non-target lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR):** Non-target lesion(s) are not considered in the definition of PR; this term does not apply.
- **irStable Disease (irSD):** Does not meet the criteria for irCR or irPD.
- **irProgressive Disease (irPD):** Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the target lesions increases by the required amount).

6.1.4.8 Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

6.1.4.9 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of all tumor lesions (target and non-target together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all target lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the SPD of the two largest perpendicular diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).

- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:

  -At least 25% increase in the SPD of all target lesions over nadir SPD calculated for the target lesions.

  -At least a 25% increase in the SPD of all target lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the target lesions.

Table 3: Immune-Related Response Criteria Definitions

Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	– 100%	irCR
Partial Response	Any	Any	Any	≥ – 50%	irPR
				< – 50% to < + 25%	irSD
				> +25%	irPD
Stable Disease	Any	Any	Any	< – 50% to < + 25%	irSD
				> + 25%	irPD
Progressive Disease	Any	Any	Any	≥ + 25%	irPD

6.1.4.10 Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

6.1.5 Response Endpoints

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

6.1.6 Additional Criteria to Continue Treatment after Progression

Patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. Patients may continue treatment with disease progression per RECIST at the discretion of the treating physician and in the absence of a declining performance status as long as there is less than 100% increase in tumor burden from beginning of treatment to the end of induction and less than 25% increase in tumor burden during maintenance ipilimumab following induction ipilimumab, inclusive of up to 4 potentially new lesions. Patients may continue to be treated in this scenario in the absence for the need for additional treatment, including any new CNS lesions that require immediate treatment. This will improve the overall assessment of the clinical activity or ipilimumab and more likely capture its true potential to induce clinical responses. Tumor assessments will be made using RECIST criteria.

6.1.7 Survival

Survival will be measured from the date of entry on study.

6.1.8 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans should be performed within 4 weeks prior to registration.
2. All patients must have a pre-dosing weight taken at every visit, as appropriate.
3. All required pretreatment laboratory studies should be done as outlined in the study calendars in Sections 7.2 and 7.3 and should be done ≤ 4 weeks before randomization.

7.2 Arms A and B: Patients Treated with Ipilimumab alone (Arm A) or Ipilimumab and Bevacizumab (Arm B)

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Time and Events Schedule	Screening: Within 4 weeks prior to Randomization	Induction Phase				Maintenance Phase		End of Treatment[I] (+/- 7 days	Follow Up[L]
		Day 1 Cycle 1 ±3 days	Day 1 Cycle 2 ±3 days	Day 1 Cycle 3 ±3 days	Day 1 Cycle 4 ±3 days	Day 1 of each cycle (+/- 7 days)	Day 1 of every 4th cycle (+/- 7 days)		
Medical History[A]	X								
Serum or urine Pregnancy Test[B]	X	X	X	X	X		X		
Physical Exam/ ECOG PS	X	X	X	X	X	X	X	X	X
Weight/Vital Signs[C]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X[H]
HIV, HBV, HCV[K]	X								
Hematology Labs[D]	X	X	X	X	X	X	X	X	
Chemistry Labs[E]	X	X	X	X	X	X	X	X	
Thyroid Function Tests[F]		X	X	X	X	X	X	X	
Urinalysis[G]	X	X	X	X	X	X	X	X	
Ipilimumab Infusion		X	X	X	X		X		
Bevacizumab Infusion[J]		X	X	X	X	X			
Adverse Event Assessment[M]		X	X	X	X	X	X	X	X
Rev. 5/15 Imaging Studies[N]	X						X[N]	X	X
BRAF Mutation Status[P]	X								
Biological Sample Submissions	See Section 7.3 and 10								
Rev. 2/17 EKG, echocardiogram	X[Q]								

[A] Medical history documented during screening should include previous toxicities from prior therapies. If the screening physical is conducted within 24 hours of dosing on Day 1, then a single examination may count as both the Screening and pre-dose evaluation.

[B] Women of child-bearing potential must have a negative serum or urine pregnancy test within 2 weeks prior to randomization for screening purposes and a negative serum or urine pregnancy test within 72 hours of each dose of ipilimumab.

[C] Vital signs will be obtained 30, 60 and 90 Minutes after the start of the Ipilimumab infusion or every 30 minutes until the infusion is complete. Vital signs should be obtained 1 hour after the infusion is complete.

[D] Hematology Labs should include CBC with differential, hemoglobin, hematocrit, white blood cells, platelets, neutrophils, lymphocytes, eosinophils and monocytes. Additional draws must be incorporated when monitoring recovery from any hematologic AE.

[E] Chemistry Labs should include albumin, amylase, lipase, BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3, calcium, and uric acid.

Rev. 8/14 **NOTE**: It is acceptable to perform a CO2 test instead of a HCO3 test as necessary.

[F] Thyroid Function Tests should include TSH and Free T4.

[G] Proteinuria will be monitored by dipstick or urine protein creatinine ratio (UPC) prior to treatment. If appropriate, 24 hour urine collection for protein may be obtained.

[H] Concomitant Medications will be collected up to 90 days from the end of study treatment.

[I] End of Study Assessment will be done within 6 weeks (±1 week) of discontinuation of study treatment.

[J] Bevacizumab should ONLY be administered in participants randomized to Arm B.

[K] At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen utilizing local standard informed consent procedures prior to this laboratory collection. These tests could be repeated later during the course of the study if clinically indicated.

[L] Every 3 months if patient is < 2 years from study entry and every 6 months if patient is 2-5 years from study entry. Patients who develop melanoma progression will be followed for survival.

[M] Adverse Events Assessment on the study will continue for all patients until 90 days after the last study drug administration. All adverse events must be collected whether they occur on treatment or non-treatment weeks and must be submitted utilizing the corresponding E3612 Adverse Event Forms, covering all time periods specified on the forms.

[N] CNS Imaging is preferred by MRI however, if an MRI is not clinically indicated, a CT of the head is allowed. Non CNS Imaging should include a chest, abdomen and pelvis CT. Imaging of other sites should be obtained when clinically indicated. If follow up scans indicate partial or complete response, a repeat confirmatory scan should be obtained in 4 weeks (but no sooner than 4 weeks).

Rev. 8/14 Patients who received prior therapy with anthracylines should have a baseline MUGA or echo with a normal ejection fraction within 28 days prior to randomization.

Rev. 8/14 Baseline imaging will be done within 4 weeks prior to randomization and then every 12 weeks (-/+ 2 weeks) if patient is < 2 years from study entry, then every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry.

Rev. 8/14 If a patient discontinues treatment for any reason other than progression, scans will be done per the standard imaging schedule above.

Rev. 8/14 [O] [Deleted in Addendum 2]

Rev. 5/15 [P] The patient's BRAF mutation status must be known (see Section 3.1.10).

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Q EKG and echocardiograms should be conducted as clinically indicated for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. For patients with evidence of CHF, MI, cardiomyopathy, or myositis, further cardiac evaluation, lab tests and cardiology consultations, including EKG, CPK, troponin, and echocardiogram, should be conducted as clinically indicated.

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7.3 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 10.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials	Prior to Start of Treatment	End of Cycle 4 (Week 12) (Induction)[4]	Day 1 Cycle 8 (Week 24) (Maintenance)[4]	End of Treatment	Submit to:
MANDATORY for *central diagnostic review*					
Tumor Tissue Biopsy (pretrial diagnostic material)[1,2]	X				CBPF
Submit from patients who answer "*yes*" to *"I agree to provide additional samples for research"*					
Tumor Tissue Biopsy[6]		X			CBPF
Peripheral Blood (ten 10cc green top heparin tubes)[3,5]	X	X	X	X	IMCPL
Peripheral Blood (one10cc red top tube)[3,5]	X	X	X	X	

1. Representative tumor tissue (block preferred) and related pathology reports and completed ECOG-ACRIN Sample Tracking System shipment manifest must be submitted for central diagnostic review within one (1) month following randomization as outlined in Section 10. Failure to submit the required materials may render the case unevaluable.
2. Tumor tissue will also be banked for future undefined research from patients who answer *"Yes"* to *"My samples and related information may be kept in a Biobank for use in future health research."*
3. Kits are being provided for the collection and shipment of the blood samples. See Section 10.3.1.1 for instructions.
4. ±3 days.
5. Please completely fill all blood tubes as full as possible.

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6. Whenever possible, biopsy of site(s) of pre-existing disease will be performed. Post-treatment biopsies, if obtained, should be performed following the induction phase (> 12 weeks from start of treatment; after all cycles of induction are completed). While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur > 14 days from last dose of bevacizumab (after all cycles of induction are completed). If for any reason removal of tissue requires a greater procedure, the biopsy must be done > 28 days from the last and > 7 days from next dose of bevacizumab. In the maintenance phase, collect biopsy post week 24; please note patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

Drug Ordering: Bristol-Myers-Squibb is supplying ipilimumab and Genentech is supplying bevacizumab, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Ipilimumab (NSC 732442) [redacted]) and Bevacizumab (NSC 704865) ([redacted] may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

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

NCI Supplied Agent(s) – General Information

NOTE: Under no circumstances can commercially supplied ipilimumab or bevacizumab be used or substituted for the NCI-supplied ipilimumab or bevacizumab, respectively.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

8.1 Ipilimumab

In this study, the investigational product is ipilimumab.

8.1.1 Drug Name

Ipilimumab (NSC 732442)

8.1.2 Other Names

Anti-CTLA-4 monoclonal antibody, MDX-010 (MDX-CTLA4, Transfectoma-derived), Yervoy®

8.1.3 Classification

Human monoclonal antibody, IgG1 subclass

M.W.: 147, 991 Daltons

Ipilimumab has two manufacturing processes- ongoing trials have been using substances manufactured using Process B. This trial, E3612, uses ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

8.1.4 Mode of Action

Ipilimumab is a recombinant human IgGI immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphtocyte 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 proliferaton. In melanoma, ipilimumab may indirectly mediate T-cell immune reponsoes against tumors. (Lexicomp, 1978-2013)

8.1.5 Storage and Stability

Ipilimumab is available in 5 mg/mL single-use vials (40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only. Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature ≥ 2°C and ≤ 8°C.

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Ipilimumab is given diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 2 mg/mL. Diluted ipilimumab solution is stable in a polyvinyl chloride (PVC), non- PVC/non DEHP (di-(2-ethylhexul) phthalate) IV bag or glass container up to 24 hours refrigerated at (2°C to 8°C) or at room temperature/ room light.

Shelf-life surveillance of the intact vials is ongoing.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Vials are for single use only. Use prepared IV solution immediately. Discard partially used vials.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

	Process C
Component	**200 mg/ vial[a]**
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

[a] Includes 2.6 mL overfill.

[b] Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

8.1.6 Dose Specifics

Induction Phase:

Ipilimumab at 3 mg/kg administered by IV infusion Day 1 Cycles 1-4

Maintenance Phase:

Ipilimumab at 3 mg/kg administered by IV infusion day 1 every 4th cycle (12 weeks) starting Cycle 8

Dose delays are allowed as per the dosing criteria. Infusions should be given over 90 minutes (not bolus or IV push).

Cycle=21 days

Calculate **Total Dose** as follows:

Patient body weight in kg x 3 mg/kg = total dose in mg

Calculate **Ipilimumab Infusion Volume** as follows:

Total dose in mg ÷ 5 mg/mL = ipilimumab volume in mL

Ipilimumab should be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL.

Calculate **Total Infusion Volume and Rate of Infusion** as follows:

Total infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min.

For example, a patient weighing 114 kg (250 lb) would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 69 mL (342 mg ÷ 5 mg/mL = 69 mL) + 273 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP at a rate of approximately 3.8 mL/min (342 mL ÷ 90 minutes) over 90 minutes.

If a subject's weight changes by > 10% during the course of the study, the ipilimumab dose should be recalculated.

8.1.7 Preparation

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an intravenous infusion using an in-line filter (pore size of 0.2 micrometer to 1.2 micrometer) and a volumetric pump, at 3 mg/kg dose, to complete the infusion in 90 minutes, with a 3-mL normal saline flush at the completion of the infusion.

- As ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
- Aseptically withdraw the required volume of ipilimumab solution into a syringe. Insert the needle at an angle into the ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial. The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
- Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
- Inject ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient. For example, if preparing a 10mg/kg treatment for a 65 kg patient you will use 4 vials of the 200 mg vial size (or 650 mg).
- If the total dose calculates to less than 90 mL of solution then the total dose needed should be diluted to at least 90 mL at a concentration between 1 mg/mL and 2 mg/mL.
- Mix by GENTLY inverting several times. DO NOT shake.
- Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
- Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

8.1.8 Route of Administration

Ipilimumab is administered as an IV infusion only. Infusions should be given over 90 minutes (not bolus or IV push). Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents.

8.1.9 Incompatibilities

No compatability information is available.

8.1.10 Availability

Bristol-Myers-Squibb is supplying ipilimumab, through the Division of Pharmaceutical Management Branch (PMB), DCTD, NCI, for this protocol.

8.1.11 Side Effects

See Section 5.3.1 (CAEPR).

8.1.12 Nursing/Patient Implications

Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes.

Ipilimumab may be excreted in milk or cross the placenta; therefore, nursing women and women with known or suspected pregnancy should not take ipilumumab.

Closely monitor patients who are on narcotics during the treatment with ipilumumab. Narcotics may mask GI signs and symptoms such as diarrhea or abdominal pain, which are relevant complications of a bowel perforation. Minor diarrhea can be a potential sign of colitis and require immediate attention

8.1.13 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

8.1.14 Ipilimumab Destruction

Partial vials can be destroyed on site per institution policy. Intact vials of the expired drug, recalled, or when protocol is closed to treatment cannot be destroyed on site without the PMB/NCI approval. If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

8.2 Bevacizumab

In this study, bevacizumab is considered an investigational agent.

8.2.1 Other names

NSC 704865, RhuMAb VEGF, Recombinant Humanized Monoclonal Anti-VEGF Antibody, Avastin

8.2.2 Classification

Antiangiogenesis agent; recombinant humanized monoclonal antibody

M.W. = 149 kilodaltons

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

8.2.3 Mechanism of Action

Bevacizumab binds Vascular Endothelial Growth Factor (VEGF) preventing the binding of VEGF to its receptors (Flt-1 and KDR), thus inhibiting endothelial cell proliferation and new blood vessel formation.

8.2.4 Dose Form

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration.

Each 400 mg (25 mg/mL - 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.

Vials do not contain a preservative and are suitable for single use only.

8.2.5 Storage/Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours. Vials must be protected from light.

8.2.6 Preparation

Opened vials must be used within 8 hours. Vials contain no preservative and are intended for single use only. Place the calculated dose of bevacizumab in 100mL of 0.9% sodium chloride for injection.

Bevacizumab should NOT be administered or mixed with dextrose solutions.

8.2.7 Dose Specifics

Induction Phase:

All patients randomized to receive bevacizumab (Arm B) will receive the drug at 15 mg/kg administered by IV infusion Day 1 Cycles 1-4

Maintenance Phase:

Bevacizumab at 15 mg/kg administered by IV infusion Day 1 of each cycle starting Cycle 5.

The dose will be calculated on the patient's actual weight. The dose will not be recalculated unless the patient has ±10% weight change.

Cycle=21 days

8.2.8 Route of Administration

Infuse the initial dose over 90 minutes. The second infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60-minute infusion is well tolerated. Monitor closely during the infusion for sign/symptoms of an infusion reaction. DO NOT ADMINISTER IV PUSH.

Once every 3 weeks, 15 mg/kg of bevacizumab will be given by IV infusion. The subject's actual weight at screening should be used to calculate the bevacizumab dose. If a subject's weight changes by > 10% during the course of the study, the bevacizumab dose should be recalculated.

A rate-regulating device should be used for all bevacizumab infusions. When the bevacizumab IV bag is empty, 50 mL of 0.9% Sodium Chloride Injection, USP, should be added to the IV bag or an additional bag should be hung. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride injection and infuse a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. The infusion should be continued for a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. If a patient experiences bevacizumab infusion-associated adverse events, patient may receive premedication at the investigators discretion prior to the next bevacizumab infusion. If premedication is required, the infusion time may not be decreased for the subsequent infusion. However, if the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes per infusion to a minimum infusion time of 30 minutes as long as the patient continues to receive the same premedication.

8.2.9 Kinetics

Estimated half-life of bevacizumab is approximately 20 days (range 11-50 days).

The clearance of bevacizumab was higher in males and in patients with a higher tumor burden.

8.2.10 Availability

Genentech is supplying Bevacizumab, through the Pharmaceutical Management Branch (PMB), DCTD, NCI, for this protocol.

8.2.11 Side Effects

See Section 5.3.2 (CAEPR)

8.2.12 Nursing/Patient Implications

- Monitor CBC and platelets. For patients on warfarin for venous access prophylaxis, routine PT monitoring.
- Monitor patient closely during infusion, for infusion related events and for bleeding.
- Monitor blood pressure prior to each dose to assess for development of hypertension.
- Instruct patient to monitor and report signs/symptoms of: bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling).
- Urine analysis for calculation of Urine Protein: Creatinine Ratio (UPC ratio) should be performed at baseline then prior to every other course of bevacizumab (or more frequently as indicated). Treatment may proceed If UPC ratio is < 3.5.

  NOTE: UPC ratio must be obtained prior to treatment. Treatment may proceed if a urine protein dip stick result is 0-1+, however the UPC ratio must still be determined. If results of urine protein dip stick are higher, hold bevacizumab until the UPC ratio is known.

UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

[urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL

[urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

Should infiltration of the bevacizumab infusion occur, the following steps are to be taken:

Discontinue the IV

If a significant volume of the bevacizumab infusion remains, restart the IV and complete the infusion.

Treat the infiltration according to institutional guidelines for infiltration of a noncaustic agent.

- Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.
- In patients with bleeding, hemostasis evaluation should be performed as clinically indicated.
- Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed.

9. Statistical Considerations

9.1 Study Design and Objectives

In this randomized phase II study, patients with advanced melanoma will be equally randomized to Arm A: Iplimumab (Ipi) or Arm B: Ipi + Bevacizumab using the stratification factors (Prior Therapy and BRAF mutation status). The stratified randomization will be based on the permuted block method.

The primary objective is to compare overall survival between Arms A vs. B. The secondary objectives are to evaluate the progression-free survival, response rate, safety and utility of immune related response criteria (irRC) in patients in Arms A vs. B.

9.2 Study Endpoints

Overall Survival (OS) is defined as the time from randomization to death from any cause. Patients who have not died will be censored at the date of last known alive.

Progression-Free Survival (PFS) is defined as the time from randomization to disease progression or death (whichever occurs first). Cases who have not had an event will be censored at the date of last disease assessment documenting the patient was free of progression. Progression will be evaluated based on international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) as described in Section 6.1.

Response will be defined by the RECIST guidelines (version 1.1) as described in Section 6.

Toxicity will be defined using the CTCAE version 4.0 criteria.

The immune response will be assessed using the utility of Immune related response criteria (irRC) as outlined in Section 6.

9.3 Sample Size Considerations and Monitoring Plan

The primary comparison will be overall survival (OS) in arms A vs. B. It will be an ITT analysis in all eligible patients. It is assumed that the median OS in patients treated in arm A will be around 11 months and the median OS will be improved to 16.5 months (50% improvement) in arm B. If the OS follows an exponential distribution, this difference corresponds to an improvement of one-year OS rate from 47% (in arm A) to 60% (in arm B).

A comparison of arms A vs. B will be made using a stratified logrank test with one-sided type I error of 10%. One interim analysis will be performed at 50% information time (57 deaths), with the final analysis at 114 deaths. To preserve the overall type I error rate, critical values at the analyses will be determined using the O'Brien and Fleming boundary. Under the accrual and failure rate assumptions below, one interim and final analyses are expected to occur at 12 and 28 months after activation. The repeated confidence interval (RCI) of Jennison-Turnbull will also be evaluated at the interim analysis. This design will provide power of 80%.

One-interim analysis conducted approximately at 50% information time will be conducted for both the efficacy and futility analysis. For the efficacy analysis,

O'Brien-Fleming boundary will be used. For the futility analysis, if the estimated hazard ratio is not trending toward in favor of alternative (i.e. estimated HR > 1) then arm B will be terminated for futility.

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Allowing for one interim analysis based on OS, a total of 160 eligible patients will be accrued and randomized to two arms and 113 deaths are expected. To account for the ineligibility rate of 5%, 168 patients will be accrued. Based on previous ECOG accrual of the same patient population, it is expected to complete the accrual in 8 months and follow patients for additional 20 months.

In addition, toxicity data will be monitored and reviewed carefully. Incidence data of specific toxicity type as well overall worst degree toxicity data will be summarized by treatment arm. The result of this analysis will be discussed with the ECOG-ACRIN DSMC Committee.

9.4 Statistical Analysis Plan

The primary and secondary efficacy (OS, PFS, Response, irRC) analyses will include all randomized patients (intent-to-treat analysis). Toxicity analysis will be based on all cases who received the treatment regardless of eligibility.

OS and PFS distributions will be estimated using the Kaplan-Meier method. The distribution of OS will be compared using the stratified log rank test with one-sided overall type I error rate of 0.100 (adjusting for the one interim analysis) and the hazard ratio of OS will be estimated using the stratified Cox proportional hazard model and one-sided 90% RCI will be constructed.

PFS distributions will be compared using the log rank test and response rates will be compared using the Chi-square or Fisher's exact test. Toxicity rate for individual AEs, categorized AEs and worst degree AEs will be compared using the Chi-square of Fisher's exact test. Two-sided p-values will be reported for these comparisons.

irRC data will be associated with the RECIST-based clinical response, PFS and OS. The method of Kaplan- Meier will be used to describe PFS and OS in each arm. The Kappa statistics which measures the degree of agreement between the RECIST-based response and irRC will be estimated. McNemar's test will be used to evaluate the agreement between irRC and RECIST-based clinical response. The landmark analysis will be conducted to evaluate the association between PFS/OS and irRC.

In the event of missing data, it will be assumed that the data will be missing at random and no imputation will be performed.

Subset analyses are planned for all stratification factors and well known prognostic factors such as age, gender, ECOG PS, LDH, etc. Subset analyses are considered to be exploratory in nature.

9.5 Gender and Ethnicity

Based on previous data from E1608 and E2603, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	59	108	167
Ethnic Category: Total of all subjects	**59**	**109**	**168**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0
White	57	109	166
Racial Category: Total of all subjects	**59**	**109**	**168**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.6 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

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10. Biological Sample Submissions

Diagnostic material from previously collected tissue must be submitted for central diagnostic review and future undefined research studies (per patient consent). Peripheral blood is to be submitted from consenting patients for future undefined research studies.

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It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 10.4). An STS shipping manifest form is to be included with every submission.

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All samples must be labeled clearly with the ECOG-ACRIN protocol number (E3612), ECOG-ACRIN patient sequence number, patient's initials, date of collection and sample type.

10.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Pretrial diagnostic pathology samples must be submitted within one (1) month of randomization and post treatment pathology samples are to be submitted within one (1) month of collection. See Section 10.2.
- Peripheral blood samples are to be submitted as outlined in Section 10.3 on the day of collection. Samples are to be collected at the following time points for each tube type:
  - Prior to start of treatment
  - End of Cycle Four (Week 12 of Induction)
  - Day One of Cycle Eight (Week 24 of Maintenance)
  - End of Treatment

10.2 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines. Submission of pretrial diagnostic pathology samples from all patients is mandatory. Failure to submit the required materials may render the patient's data unevaluable.

The tissue samples are to be labeled with the Pathology ID as well as the information above.

10.2.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest form.
  - If STS is unavailable, complete ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse). Please log information into STS once accessible.
- Copy of the pathology report.

Pathological Material Submission:

- Representative diagnostic FFPE tumor tissue blocks

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NOTE: Whenever possible biopsy of site(s) of pre-existing disease will be performed. Post-treatment biopsies, if obtained, should be performed following the induction phase (>12 weeks from start of treatment; after all cycles of induction are completed). While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur >14 days from last dose of bevacizumab (after all cycles of induction are completed). If for any reason removal of tissue requires a greater procedure, the biopsy must be done >28 days from the last and >7 days from next dose of bevacizumab. In the maintenance phase, collect biopsy post week 24; please note patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.

NOTE: If a block is unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirement:

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- One (1) H&E slide from each source block, and
- Twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor, and
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (1-844-744-2420). Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.2.2 Shipping Procedures

Pathology materials are to be shipped at ambient temperature within one (1) month following patient randomization or collection.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Ship to:

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ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Pretrial diagnostic pathology materials will be forwarded to Dr. [redacted] by the CBPF for central review.

10.3 Submissions to Immunologic Monitoring and Cellular Products Laboratory (IMCPL)

Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact the ECOG-ACRIN Study Coordinator at (412) 624-0078 at the IMCPL.

NOTE: Blood should **NOT** be collected on Fridays.

Instructions to order kits are outlined in Section 10.3.1.1

Submit from patients who answer "Yes" to "I agree to provide additional samples for research."

10.3.1 Sample Preparation Guidelines

Please completely fill all blood tubes as full as possible and collect the correct number and tube type as outlined below. Each tube must be clearly labeled to include:

- ECOG-ACRIN protocol number E3612
- ECOG-ACRIN five-digit patient sequence number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

At EACH time point please submit the following:

- One (1) FULL 10 cc RED top tubes (BD cat #367820 or SST 367988 gel separator/gold top/ tiger tubes if the center can centrifuge them)
- Ten (10) FULL 10 cc GREEN top heparin tubes (BD cat # 366480)

10.3.1.1 Shipping Kits

Shipping kits are available to order for the collection of the blood samples, and will contain the supplies and instructions for collecting, processing, and shipping the samples. To order kits please fax the request using Shipping Kit Request Facsimile Form (Appendix VI) to (412) 623-6625 or call the IMCPL at (412) 624-0078. Please allow ten (10) working days for shipment and provide the following information:

- Study Number
- Participating Site Number
- Contact Person and Telephone Number

The kits will be shipped via FedEx Express Saver. Please plan ahead, **priority overnight shipment is not possible.**

All blood samples should be shipped the day of collection using the shipping kit. Follow the shipping instructions provided in the kit carefully.

The shipping kit consists of the following:

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- Insulated shipping container and packing material
- FedEx Priority Overnight return label
- Shipping instructions
- Shipping Kit Request Form

10.3.2 Shipping Procedures

Blood collected into the appropriate tubes should be sealed, wrapped and placed in the specimen shipper kit and shipped on the same day they are drawn by Federal Express Priority Overnight courier using the return label provided in the kit. The green top tubes should be shipped at ambient temperature (no wet or dry ice) and the red top tubes should be refrigerated immediately and shipped at 2-8ºC. Shipments must be timed to arrive during normal working hours and should be shipped in one box.

The laboratory will be open Monday through Friday to receive samples. Do NOT ship on Fridays or Saturdays, or the day before a legal holiday. Ship by overnight courier Monday - Thursday only to:

Immunologic Monitoring and Cellular Products Laboratory
University of Pittsburgh Cancer Institute
UPCI-IMCPL
ECOG-ACRIN Study Coordinator
Hillman Cancer Center
5117 Centre Avenue, L 1.26
Pittsburgh, PA 15213
Tel: (412) 624-0078
FAX: (412) 623-6625

Federal Guidelines for the Shipment of Blood Products: Sites should follow IATA regulations for Packaging UN3372 shipments. Please refer to FedEx guidelines.

An STS shipping manifest form must be generated and shipped with all sample submissions.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

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Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory. For specimen submissions to the IMCPL, notify the ECOG-ACRIN Study Coordinator by FAX (412) 623-6625 using the Specimen Shipment Requisition Form (Appendix VII). If you are unable to get through to the laboratory by FAX, telephone the ECOG-ACRIN Study Coordinator at (412) 624-0078 and provide the tracking number. Indicate the appropriate Lab ID# on the submission form:

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- ECOG-ACRIN CBPF
- ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Use of Specimens in Research

Pathological materials will be distributed to investigators for central diagnostic review.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies, including residuals from the mandatory diagnostic review, will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN and the ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Electronic Data Capture

Please refer to the E3612 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

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A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. List of Required Materials for E3612
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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List of Required Material

E3612: A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

The following materials are to be submitted within one (1) month of randomizing the patient to the trial or within one (1) month of collection:

1. Required Diagnostic Materials

   - Pretrial Diagnostic Pathology Materials (MANDATORY): Representative diagnostic tumor tissue blocks
   - Post Treatment Tumor Biopsy (If performed, samples are to be submitted from consenting patients)

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NOTE: Whenever possible biopsy of site(s) of pre-existing disease will be performed. Post-treatment biopsies, if obtained, should be performed following the induction phase (> 12 weeks from start of treatment; after all cycles of induction are completed). While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur > 14 days from last dose of bevacizumab (after all cycles of induction are completed). If for any reason removal of tissue requires a greater procedure, the biopsy must be done > 28 days from the last and > 7 days from next dose of bevacizumab. In the maintenance phase, collect biopsy post week 24; please note patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.

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NOTE: **If a block is unavailable for submission**, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF 1-844-744-2420.
- One (1) H&E slide from each source block, and
- Twenty (20) 5 µm unstained, uncharged air-dried plus slides from the thickest part of the tumor,

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (eacbpf@mdanderson.org) to obtain alternative submission requirements.

2. Forms and Reports:

NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including site pathologists).

The following items are to be included with the pathology materials:

- Institutional Pathology Report
- Sample Tracking System (STS) Shipping Manifest Form

3. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites) or by fax 713-563-6506.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

[redacted] MD, and [redacted] MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: [redacted], M.D., Chair

DATE: _____

SUBJECT: Submission of Pathology Materials for E3612: A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

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The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and future undefined research studies.

Keep a copy of the submission for your records and return the surgical pathology report(s), the slides and/or blocks and any other forms and required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites) or FAX 713-563-6506.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

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A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

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Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Appendix III

CRADA/CTA

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agent, each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.”):
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborators for advisory review and comment prior to submission for publication. Collaborators will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborators for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix V

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Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Ipilimumab or Bevacizumab, or within 28 days of the patient's last dose of Ipilimumab or Bevacizumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

- The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office - Boston. Please contact the ECOG-ACRIN Operations Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if

the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss Death

A pregnancy loss death is defined in CTCAE as “A death in utero.”

It must be reported via CTEP-AERS as Grade 4 “Pregnancy, loss” under the System Organ Class (SOC) “Pregnancy, puerperium and perinatal conditions”.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Rev Add8 **Reporting a Neonatal Death**

A neonatal death is defined in CTCAE as “A death occurring during the first 28 days after birth” that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Ipilimumab or Bevacizumab must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 “Neonatal loss”under the System Organ Class (SOC) “General disorder and administration site conditions”.

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VI

Shipping Kit Request Facsimile Form

ECOG-ACRIN PROTOCOL E3612

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.26 5117 Centre Avenue Pittsburgh, PA 15213-1863 Telephone: 412-624-0078 FAX: 412-623-6625

To: ECOG-ACRIN Study Coordinator Fax: 412-623-6625

From: Name:_____

Institution:_____

Telephone: _____

Fax: _____

Number of Kits Requested:

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Shipping Address: _____

_____

_____

PLEASE ALLOW 10 WORKING DAYS FOR RECEIPT OF SHIPPING KITS

NOTE: To order collection and shipping kits for E3612, patients must be registered to or in the process of being worked up for the E3612 trial. Due to funding restrictions institutions cannot order multiple collection and shipping kits in advance.

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Appendix VII

Specimen Shipment Requisition Form

ECOG-ACRIN – PROTOCOL E3612

It is required that samples submitted from patients participating in E3612 be entered and tracked via the online ECOG-ACRIN Sample Tracking System. This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Immunologic Monitoring and Cellular Products Laboratory	UPCI Research Pavilion at the Hillman Cancer Center Room L 1.26 5117 Centre Avenue Pittsburgh, PA 15213-1863 Telephone: 412-624-0078 FAX: 412-623-6625

Ship samples by FedEx Priority Overnight to arrive the next morning unless otherwise directed by the protocol. Do NOT ship on Friday or Saturday, or the day before a legal holiday.

Call the IMCPL ECOG-ACRIN Study Coordinator at 412-624-0078 with questions on collection and shipping.

Please complete the following information and include this form in the shipment.

ECOG-ACRIN Patient Sequence Number: _____

ECOG-ACRIN Patient Initials: _____
Last First

Clinical Site:_____

Site Contact: _____

Telephone Number: _____

Fax Number: _____

Federal Express® Air Bill No.: _____

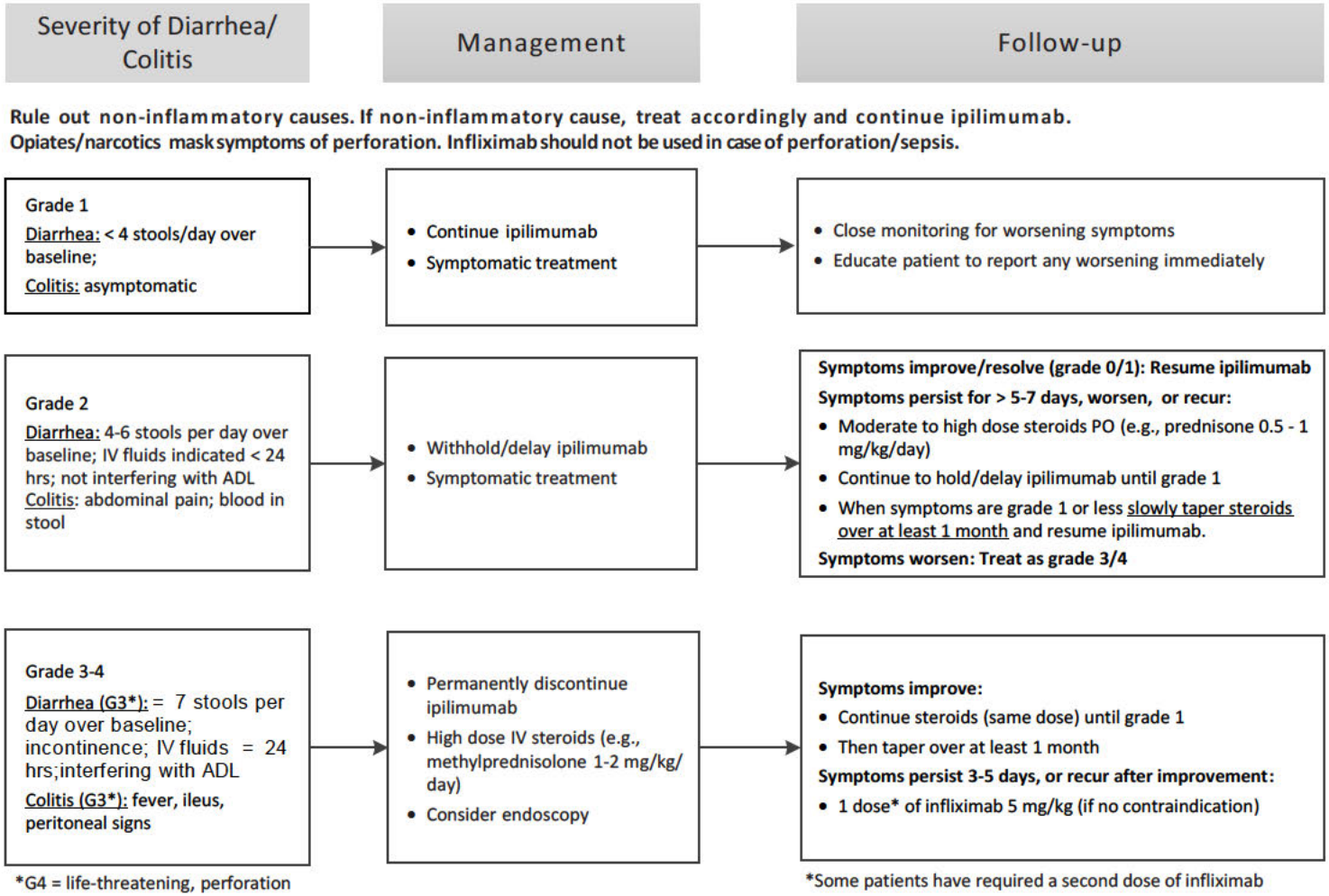
Date of Shipment: _____

Specimen Collection Date ___/___/___
MM/DD/YY

Specimen Collection Time: ____ ____:____ ____
(24 hour clock)

A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Appendix VIII
GI Toxicity Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO Cortic osteroids.

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Appendix IX
Hepatotoxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.
Caution: Infliximab is contraindicated in hepatic insufficiency

Severity of Hepatitis	Management	Follow-up
Grade 1 AST or ALT = 3.0 x ULN **and/or** Total bilirubin = 1.5 x ULN	• Continue ipilimumab	• Continue monitoring LFT prior to each dose
Grade 2 AST or ALT > 3 0 to = 5.0 x ULN **and/or** Total bilirubin > 1 5 to = 3.0 x ULN	• Increase frequency of monitoring (q3d) • Withhold/delay ipilimumab while investigating alternative etiology	**Return to baseline** • Resume q3w monitoring • Resume ipilimumab **Elevations persist for > 5-7 days or worsen, and no alternative etiologies are identified** • Consider moderate to high dose steroids PO (e g., 0.5- 1 mg/kg/day prednisone or equivalent)
Grade 3-4 AST or ALT > 5.0 x ULN **and/or** Total bilirubin > 3.0 ULN	• Discontinue ipilimumab* • Increase frequency of monitoring (q1-3d) • High dose IV steroids (e g., methylprednisolone 1-2 mg/kg/day**)	**AST/ALT/Tbili return to grade 2** • Taper steroids over at least 1 month **Labs do not decrease over 3-5 days, worsen or rebound:** • Add MMF*** 1 g BID • If no response within 3-5 days, consider other immunosuppressants per local guidelines

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* Ipilimumab may be held/delayed rather than discontinued if AST/ALT = 8 x ULN and Tbili = 5 x ULN. Resume ipilimumab when AST/ALT/Tbili return to grade 2 and meet protocol specific retreatment criteria.

** The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

***MMF, mycophenolate mofetil

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

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Appendix X
Skin Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

Severity of Skin Toxicity	Management	Follow-up
Grade 1-2	• Symptomatic therapy, e.g. antihistamines, topical steroids • Continue ipilimumab	**Symptoms resolve: Continue ipilimumab** **Symptoms persist > 1-2 weeks or recur:** • Continue Ipilimumab • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Once controlled, taper steroids over at least 1 month
Grade 3-4	• Hold/delay ipilimumab (regardless of relationship) • Take photos of rash • Consider skin biopsy • Dermatology consult • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day)	**Symptoms resolve / return to grade 1:** • Taper steroids over at least 1 month • Resume ipilimumab if grade 3 • Discontinue if grade 4 toxicity considered related

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO cortic osteroids.

A Randomized Phase II Trial of Ipilimumab with or without Bevacizumab in Patients with Unresectable Stage III or Stage IV Melanoma

Appendix XI
Neurological Toxicity Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.
Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.

Severity of Neurological Toxicity	Management	Follow-up
Grade 1	• Continue ipilimumab	Continue monitoring the patient. If symptoms worsen, treat as below.
Grade 2	• Hold/delay ipilimumab • Treat symptoms per local guidelines	Resume ipilimumab when resolved / grade 1 If symptoms worsen, treat as below.
Grade 3-4 sensory	• Discontinue ipilmumab if considered related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/ kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month
Grade 3-4 motor	• Discontinue ipilimumab regardless of relationship • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month **Symptoms do not resolve or progress; atypical presention:** • Consider IVIg or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

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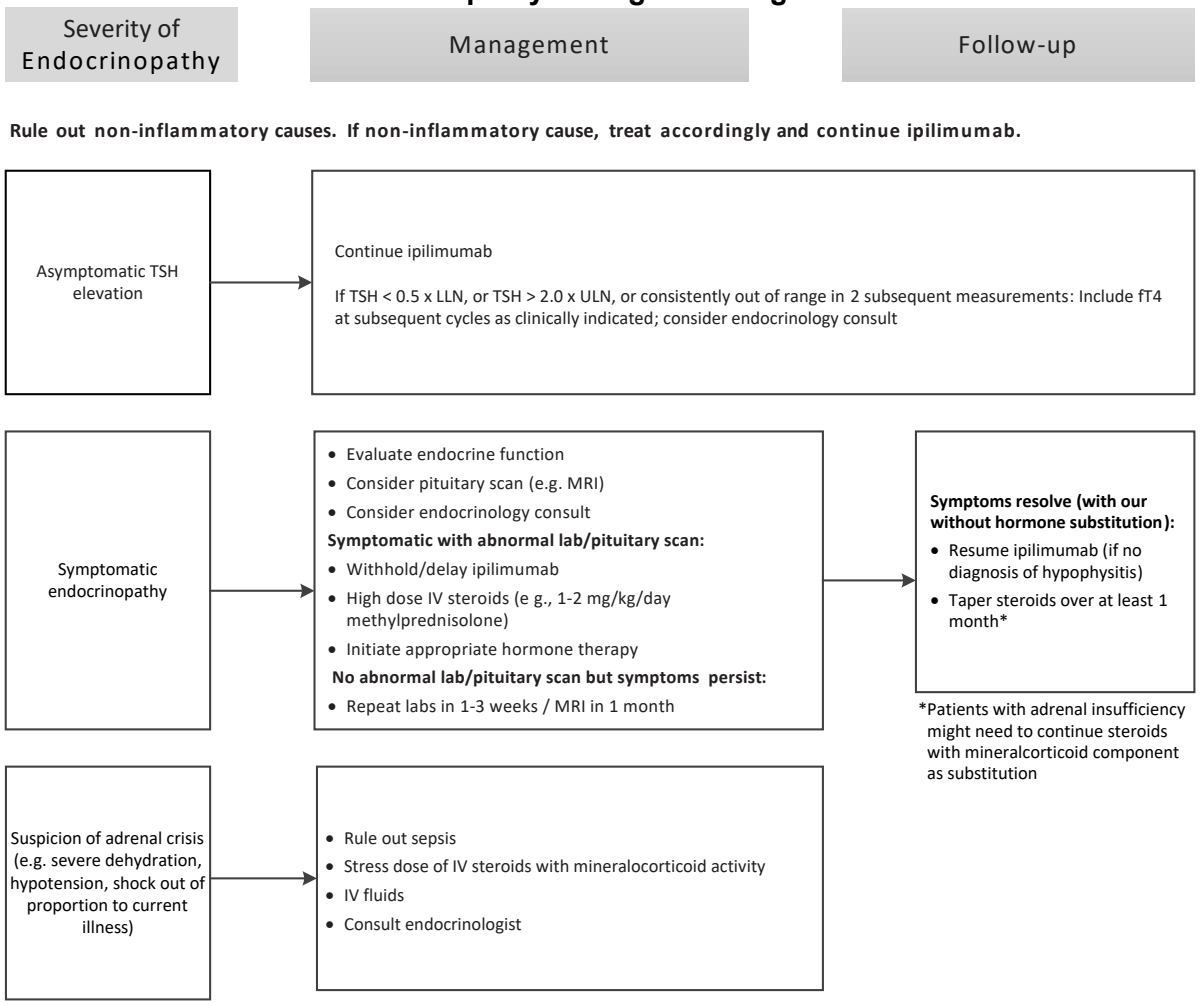
Appendix XII
Endocrinopathy Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.