March 2, 2016

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Dear Ms. Kruhm:

Enclosed is Addendum #5 to E3611, *A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma.*

This amendment is in response to Drs. Howard Streicher, James Zwiebel, and Meg Mooney's Request for Rapid Amendment on March 1, 2016.

The following revisions to E3611 protocol have been made in this addendum:

	Section	**Change**
1.	Cover page	Updated version date
2.	Section 5.3	Replaced ipilimumab CAEPR with updated Version 2.7, June 28, 2015

The following revisions to E3611 Informed Consent Document have been made in this addendum:

	Section	**Change**
1.	Cover page	Updated version date
2.	"Non immune-based Risks Associated with Ipilimumab"	Removed instructional text titled "Please note the following in reviewing these risks" and replaced condensed risk list with updated Version 2.7, June 28, 2015

If you have any questions regarding this addendum, please contact li.amy@jimmy.harvard.edu or 617-632-3610.

We request review and approval of this addendum to E3611 so ECOG-ACRIN may activate it promptly.

Thank you.

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Sincerely,

Pamela Cogliano

Protocol Development Manager

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

E3611

A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

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MELANOMA COMMITTEE CHAIR: John M Kirkwood, MD

Version Date: March 2, 2016

STUDY PARTICIPANTS
US Sites Only

ACTIVATION DATE
December 27, 2012
Addendum #1 – Incorporated prior to activation
Addendum #2 – 5/14
Addendum #3 - 10/14
Addendum #4 - 4/15
Addendum #5 – 3/16

Agents	IND#	NSC#	Supply
Ipilimumab	10200	732442	NCI Supplied
Interferon		377523	Commercial

Table of Contents

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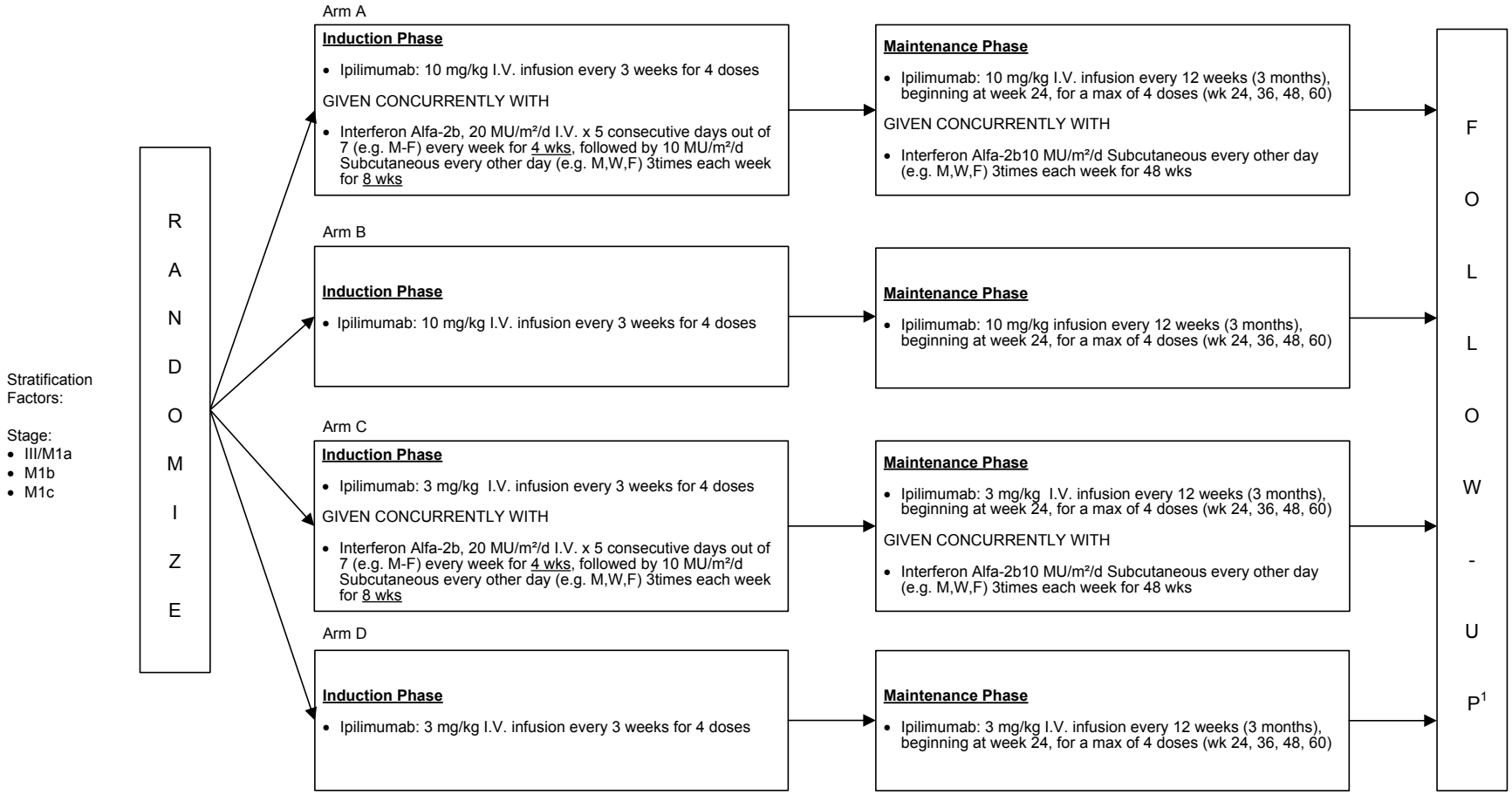


Accrual Goal: 88

[1]Long term follow up until disease progression

1. Introduction

1.1 Management of Metastatic Melanoma and the Role of CTLA4 Blockade

Advances in the preceding few years have brought deepening and exciting understanding to the molecular biology of melanoma and the immune regulatory mechanisms that play an important role in the oncogenesis of this disease and the host immune tolerance conducive to disease progression. As a result, therapeutic options against melanoma has expanded to include several promising agents that exploit various targets that the melanoma cell is dependent upon for survival. Recent trials involving the CTLA-4 blocking antibody ipilimumab and the BRAF inhibitor vemurafenib have produced exciting results leading to regulatory approval of both agents as standard of care treatment options in the metastatic setting, while their use in the adjuvant setting is a topic of ongoing investigation. Therapeutic options outside of clinical trials for melanoma have had limited benefits and no known survival advantage until the approval of ipilimumab and vemurafenib in 2011.(1, 2) Immunotherapy utilizing interleukin-2 (IL-2) (for metastatic melanoma) and interferon (IFN)-α (for resected high risk melanoma) have produced the most promising and durable results, albeit in subgroups of patients only.(3)

By the time melanoma has become clinically detectable, the theory of immunoediting holds that the tumor has already evolved mechanisms to evade the host immune response. Anti-CTLA4 therapy has a novel mechanism of action, unlocking the immune response by disrupting the CTLA4 checkpoint, a key regulator of T-cell activity that appears to play an important role in maintaining tolerance.(4) CTLA4 blocking antibodies (ipilimumab and tremelimumab) have shown promising and durable activity as monotherapy in a fraction of patients.(5) The ipilimumab-Gp100, MDX-1020, phase III study that lead to the recent FDA approval of ipilimumab at 3 mg/kg for advanced inoperable melanoma demonstrated significant OS prolongation in favor of ipilimumab.(6) More recently, the MDX-024 phase III trial showed that ipilimumab at 10 mg/kg plus dacarbazine has significant survival benefit over dacarbazine alone as first-line treatment in metastatic melanoma.(7) Tremelimumab has shown promising clinical activity in earlier trials testing this anti-CTLA4 blocking antibody in pretreated advanced melanoma (A3671008) and in phase III clinical trial (A3671009) that enrolled 655 patients with treatment-naive advanced melanoma and compared tremelimumab to dacarbazine or temozolomide.(8) Although this study was halted for futility, the majority of responses to tremelimumab were durable and median survival was12 months. These efforts utilizing CTLA4 blockade to harness the immune system to target melanoma have had tremendous potential and have lead to significant progress, but also face daunting challenges reflected by the limited clinical benefits seen with monotherapy, overall and where there is room for major improvements in the magnitude of benefits derived and their durability. Although very promising, the benefits of ipilimumab monotherapy have been limited and it has become obvious that the future of melanoma therapy resides in rational combinations that build upon the promise of single agent activity with such agents as IFN-α that currently hold the most durable adjuvant immunotherapeutic survival benefits.

1.2 IFNα-2b and the Role of High-Dose IFN-α2b (HDI) as Adjuvant Therapy for High-risk Resected Melanoma

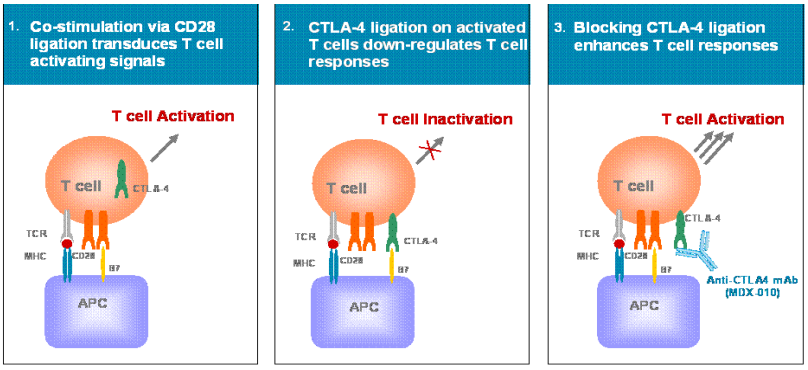
IFNα-2b, a type-I IFN, has potent immunoregulatory, antiproliferative, differentiation-inducing, apoptotic, and anti-angiogenic properties in a variety of malignancies.(9) IFN-α at high dosage (HDI) has been shown to play a critical role in interrupting tumor immune tolerance both improving tumor immunogenicity and increasing dendritic cell (DC) activation and survival.(9, 10) IFN-α upregulates major histocompatibility complex (MHC) antigen processing and costimulatory molecules leading to more efficient antigen presentation that may elicit previously low-affinity autoreactive T-cells.(9, 10) IFN-α has been reported to affect almost all stages of myeloid DC generation, maturation, differentiation and function(11) increase activation and survival of DCs, which in turn promote maturation of effector CD8 T cells.(9, 10) Therefore, IFN-α has a potentially significant impact on tumor and antigen-presenting cells (APCs) by making the tumor more immunogenic and enhancing antigen cross presentation, jointly leading to better anti-tumor immunization. Moreover, in their immature state, IFN-treated DCs induce a 'polarized' Th1 cytokine microenvironment.(12) Similarly, IFNs polarize lymphocytes towards the pro-inflammatory Th1 phenotype.(13-15) This may promote a significant impact of type-I IFNs in the cytotoxic T cell compartment, inducing potent antitumor cell-mediated cytotoxicity(16), and promoting natural killer (NK) cell-mediated proliferation and cytotoxicity.(17) Type-I IFNs have been shown to activate APCs to produce chemokines that differentiate naïve CD4 T-cells, expand non-polarized antigen-primed Th1 T-cells, and cooperate with NK cells to induce anti-tumor CD8 T-cells to create a polarized Th1-biased tumor micro-environment in which host effector response against melanoma is possible.(18) This IFN-induced Th1 bias can be detected in melanoma patient circulation as an upregulation of the pro-inflammatory cytokine response (Th1 polarization) as demonstrated in the adjuvant E1694 trial.(19) In addition, locally produced type-I IFNs induce the expression of integrins and chemokine receptors and recruitment of natural killer cells and macrophages leading to Th1 rather than Th2 lymphocyte traffic to the tumor site.(18) This has been demonstrated clinically where responding patients had significantly greater increases in intra-tumor CD11c+ DCs and CD3+ T-cells in a neoadjuvant melanoma study of HDI.(20) Therefore, IFN-α induces a Th1 shift in immunity, promotes antitumor cell-mediated cytotoxicity and attracts Th1 lymphocyte traffic to the tumor, while increasing cellular expression of MHC, making tumor cells better targets for cell-mediated immune attack.

Clinically, three national cooperative group studies have evaluated the benefit of HDI as adjuvant therapy for resectable cutaneous melanoma that is at high-risk for recurrence and death. These included patients with regional lymph node metastases (T_{1-4}, N_1, M_0) and primary localized deep melanomas (T_4, N_0, M_0) that have a 5-year post-surgical relapse rate of more than 40-50%. The HDI treatment regimen is comprised of daily intravenous IFN-α2b at 20 MU/m² given for 5/7days for 4 weeks followed by a self-administered subcutaneous phase of 10 MU/m² TIW for 48 weeks. The first and third of these studies both demonstrated significant relapse free as well as overall survival prolongation, compared to observation (E1684) and compared to a vaccine (GMK) that was selected as the optimal vaccine candidate at the time (E1694). The second trial, E1690, conducted in part before and in part after the approval of HDI, was associated with systematic crossover of patients from the observation-assigned

arm to treatment at nodal relapse with HDI. This trial showed significant differences in terms of relapse-free but not overall survival.(21-23) The most recently reported intergroup adjuvant trial, E1694, tested HDI in relation to the GMK vaccine, for which outcome results appeared nearly identical to the prior E1690 observation arm, which was unblinded and reported when mortality and relapse frequencies observed with GMK proved to be significantly higher (RFS HR = 1.49; OS HR = 1.38) than with HDI. Thus, the published literature contains three RCT reports of relapse-free survival benefit and two RCT reports of overall survival benefit of HDI that have yet to be equaled by any other therapy available for high-risk melanoma. The advantage for patients treated with HDI amounts to a relapse frequency reduction of 24-38% and mortality reduction of 22-32% based upon the hazard ratios for patients treated with HDI or observation, or the vaccine (GMK).

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).(24) (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.(25) The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.(26, 27) 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.(28, 29) 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.(30) 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.(31) 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.(32-35) Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro.(33) Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation.(36-38) 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.(35)

1.4 Summary of Results of Investigational Program of Ipilimumab

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 of Ipilimumab

1.4.3.1 Mechanism of Action of Ipilimumab

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.

1.4.3.2 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

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/m2 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.

Safety Profile of Ipilimumab at a Dose of 10 mg/kg (Phase 2 data)

The safety profile of ipilimumab at a dose of 10 mg/kg was characterized in a total of 325 subjects who received multiple doses of 10 mg/kg ipilimumab as monotherapy in the 4 completed melanoma studies (CA184004, -007, -008, and -022). Overall, the incidence of Grade 3/4 AEs attributable to study drug was 31%. The target organ system, the incidence and the severity of the most commonly observed irAEs are displayed in Table 4.

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.

Rev. 5/14

Updated data provided by BMS from a pooled analysis of phase II studies of ipilimumab 10 mg/kg, multiple doses, including studies CA184004, CA184007, CA184008, CA184022 and CA184042, reviewed AEs from 353 patients treated with ipilimumab 10 mg/kg. A total of 10 related deaths were reported and at least 7 were considered irAE. These cases included colon perforation, multiorgan failure/disease progression, Grade 3 hypophysitis/disease progression, acute myeloid leukemia, acute glomerulonephritis, hypovolemic shock, liver dysfunction, Grade 3 AST increase/unknown cause of death, Grade 2 enterocolitis/disease progression, Grade 4 septic shock/Disease. In 3 cases, it was determined that the AE management algorithms were not followed:

- Colon perforation (patient treated with pulse steroids; no high dose steroids and no taper).

- Liver dysfunction (patient received ipilimumab in the setting of severe liver dysfunction).
- Gr2 enterocolitis (treated with prednisone and rapid taper. Patient died of disease progression but the enterocolitis was still ongoing at that time).

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 After Exposure to Ipilimumab

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 seizures and delivered the baby at 36 weeks gestation. The baby had respiratory complications that resolved by birth week 16. Three (3) of the 4 partners of male study subjects had full term, normal babies. The fourth baby had small ureters, which are expected to grow as the baby matures. 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 7. 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.

1.4.5.1 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.

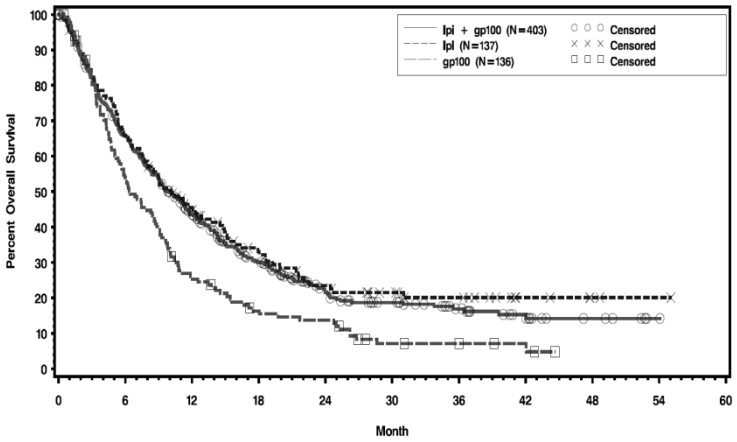
The major efficacy outcome measure was overall survival (OS) in the ipilimumab + gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the ipilimumab + gp100 arm compared to the ipilimumab arm, OS in the ipilimumab arm compared to the gp100 arm, best overall response 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.

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

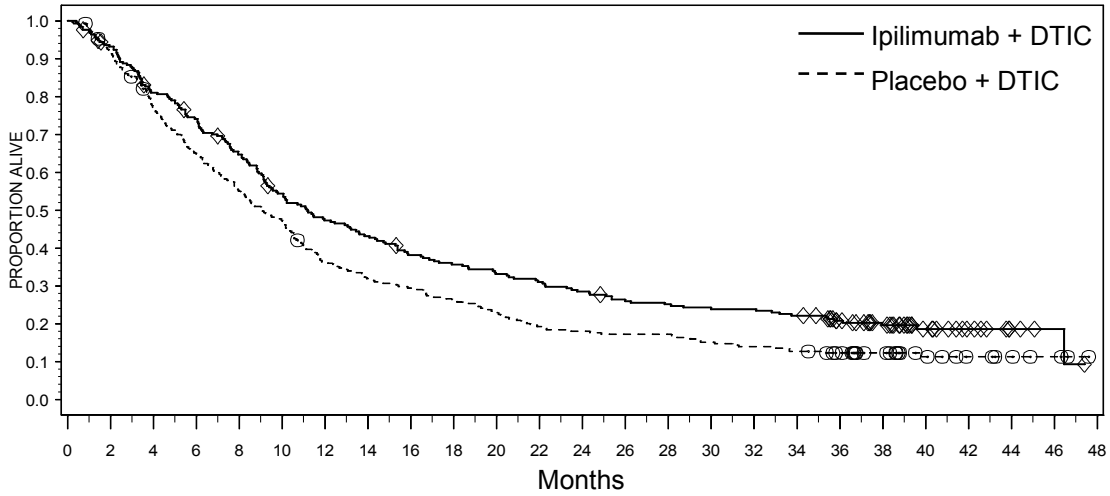
CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m2 q3w, with either ipilimumab 10 mg/kg or placebo cycles 1-4, and as maintenance after 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

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

1.4.5.3 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.

1.4.5.4 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	--/N/A	--/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 Overall Risk/Benefit Assessment of Ipilimumab Studies

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.

1.6 A phase II study of tremelimumab combined with HDI for metastatic melanoma

A phase II study testing the combination the anti-CTLA4 blocking monoclonal antibody tremelimumab and HDI was conducted in metastatic melanoma.(39) Tremelimumab was given at 15 mg/kg IV/course q12 wks. HDI was given concurrently including IV induction at 20 MU/m^2 IV, 5 d/wk x 4 wks followed by maintenance at 10 MU/m^2 SC TIW, for 8 wks/course. From course 2 onward, HDI maintenance was given SC. Dose delays were allowed for tremelimumab, and if HDI was tolerable with dose modification patients continued HDI even if tremelimumab was discontinued. A 2-stage design was adopted.

At the completion of stage 1 accrual, 16 patients were enrolled. All had AJCC stage IV melanoma (4 M1a, 2 M1b, 10 M1c) and all had previously received therapy for metastatic disease (range 1-5 prior regimens). Two patients had previously treated stable brain metastases. A total of 24 courses have been administered (median of 1 course per patient; 6 patients continue on therapy). The frequency of grade 3/4 toxicities did not exceed experience with the FDA-approved HDI regimen alone. Grade 3/4 toxicities included neutropenia (3 patients; 19%), hepatic enzyme elevations >5 fold ULN (2; 13%), fatigue (6; 38%), anxiety (2; 13%). One patient had grade 4 autoimmune colitis leading to treatment discontinuation, but recovered completely following steroid therapy. The overall response rate was 19% (3 partial responses lasting 2+ - 4+ months). Responses were seen in both M1a (1) and M1c (2) disease. Two of the PRs were associated with autoimmune manifestations (autoimmune colitis and marked vitiligo). Six patients have stable disease lasting 1+ - 4.5 months and 3 have had progression.(40, 41)

The study completed accrual (stages I and II) with 37 patients enrolled, median age 58 (28-76). All subjects had AJCC stage IV (9 M1a, 6 M1b, 22 M1c) and most had previously received therapy (0-5 regimens). Two patients had prior treated brain metastases. Seventy two courses of tremelimumab have been administered as of the data cut-off date (average 2/pt). Grade 3/4 toxicities included neutropenia (6 pts; 17%), diarrhea/colitis (4; 11%), liver enzyme elevation (4; 11%), rash (4; 11%), fatigue (15; 40%), anxiety/depression (5; 14%). Autoimmune toxicities due to tremelimumab were successfully managed with steroids. Table 10 summarizes the adverse event profile.

Response data were available for 35 patients. Best OR rate (RECIST) was 26% (90%CI=0.14-0.38) (4CR and 5PR lasting 6, 6, 12+, 14+, 18+, 20, 28+, 30, 37+ months). By intent to treat (N=37), the response rate was 24% (90%CI=13%-36%). Fourteen patients (38%) had SD lasting up to 21 months. Among these 9 responders, 4 had prior adjuvant IFN-α. Seven patients had prior high dose IL-2, but none of these patients had a response on this study. Tables 11 and 12 summarize tumor response data and the durability of the responses.

Median PFS was 6.4 months (95%CI = 3.3-12.1 months). Median OS was 21 months (95%CI=9.5,-). Conducting an exploratory analysis utilizing the model proposed by Korn et. al., the predicted 1-year OS rate was 21% while the observed rate was 62% (95% CI = 46%, 78%); p <.0001.(42) Please see Figures 4 and 5 and Table 13.

There was significant association between therapy-induced autoimmunity and clinical benefit (CR/PR/SD;P=0.0059). Lower baseline C-reactive protein (CRP ≤ 2.7ULN) was associated with clinical benefit (p=0.0494) and improved probability

of survival (p=0.0032). Higher absolute lymphocyte count at baseline was associated with response (CR/PR;p=0.0183) and clinical benefit (CR/PR/SD;p=0.0255). However, biomarker associations were not significant (P>.05) after adjusting for multiple comparisons.

These results compare favorably to monotherapy with HDI, tremelimumab(43) or ipilimumab.(6) IFN-α was the first recombinant cytokine to be investigated for the therapy of metastatic melanoma yielding response rates of about 16%. However, the median duration of response was only about 4 months. The ipilimumab-Gp100 phase III study that lead to recent FDA approval of ipilimumab for metastatic melanoma randomized 676 pretreated patients. The RR was 5.7% (ipilimumab+gp100), 10.9% (ipilimumab+placebo), 1.5% (gp100+placebo). Median OS was 10.0 months (ipilimumab+gp100), 10.1 months (ipilimumab+placebo), 6.4 months (gp100+placebo). The 1-year survival rates were 44% (ipilimumab+gp100), 46% (ipilimumab+placebo), 25% (gp100 + placebo).(6) Our data in this study also compare favorably to the MDX-024 phase III trial where ipilimumab plus dacarbazine had a significant survival benefit over dacarbazine alone as first-line treatment in metastatic melanoma (median OS 11.2 vs. 9.1 months, median PFS 2.8 vs. 2.6 months, RR 15% vs. 10%).(7) Tremelimumab at 15 mg/kg every 90 days (up to 4 cycles) was tested in a second line phase II study (A3671008) in inoperable, AJCC stage III/IV melanoma (N=246).(44) The objective RR was 7%, median OS 10.1 months and the one-year survival rate was 41%.(44) In a subsequent phase III trial (A3671009) in treatment-naive advanced melanoma comparing tremelimumab to dacarbazine/temozolomide, median OS was 11.8 months.(8) In terms of safety, the results of this study that tested the combination of HDI and tremelimumab at 15 mg/kg are comparable to other studies testing anti-CTLA4 monoclonal antibody therapy, as summarized in **Table 14**.

Therefore, this study has met the phase II criteria for safety and efficacy. The combination of HDI and tremelimumab had tolerable and manageable toxicity in relation to the therapeutic benefit observed. Testing in a randomized setting is therefore now warranted. Given the interval FDA approval of ipilimumab for therapy of advanced melanoma, this study would by extension argue for evaluation of ipilimumab in combination with IFN-α in a randomized phase II study.

Figure 4. Kaplan – Meier plot of the probability of progression-free survival (N=37). The estimated median is 6.4 months (95% Confidence Interval = 3.3, 12.1).

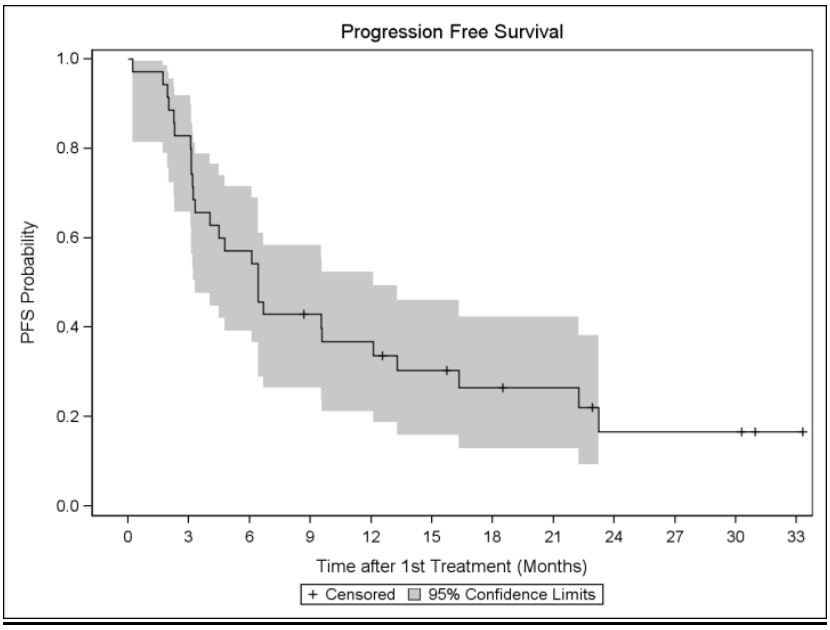


Figure 5. Kaplan – Meier plot of the probability of overall survival (N=37). The estimated median is 21 months (95% Confidence Interval = 9.5 months, -).

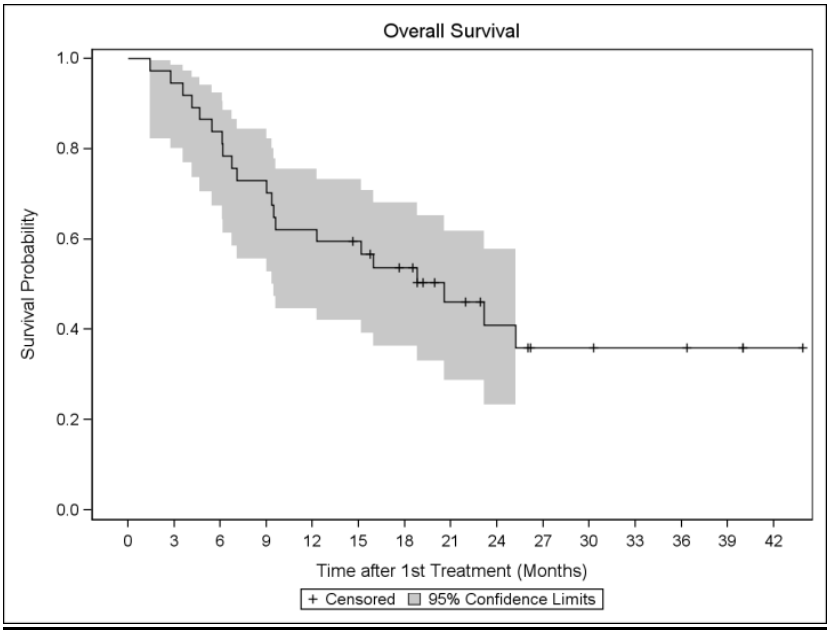


Table 10. Adverse events considered possibly, probably or definitely related to the study regimen (CTCAE v.3)						
Type	**All Grades**		**Grade 3**		**Grade 4**	
	No. Patients	**%**	**No. Patients**	**%**	**No. Patients**	**%**
Immune mediated						
Diarrhea/Colitis	21	57.0	3	8.0	1	2.7
Hyper/pothyroidism	2	5.4	0	0	0	0
Hypogonadism	1	2.7	0	0	0	0
Hepatitis-Increased AST/ALT/AP/GGT	8	21.6	3	8.0	1 (GGT)	2.7
Skin rash	23	62.0	4	11.0	0	0
Constitutional						
Fatigue	37	100	15	40.5	0	0
Gastrointestinal						
Nausea	27	73.0	1	2.7	0	0
Vomiting	17	46.0	1	2.7	0	0
Hematologic						
Neutropenia	19	51.4	5	13.5	1	2.7
Neuro-Psychiatric						
Depression/Anxiety	9	24.3	4	11.0	0	0
Renal						
Increased Creatinine/dehydration	2	5.4	1	2.7	0	0
Respiratory						
Bronchospasm	1	2.7	1	2.7	0	0
Other						
Cardiac arrhythmia (atrial fibrillation)	1	2.7	1	2.7	0	0
Increased CPK	9	24.3	2	5.4	1	2.7

Table 11. Efficacy Summary (Stage I + II): Best response based on 37 patients enrolled (Intent To Treat)

		No. Pts	Duration (month)	Primary No. Pts (%)			Classification No. Pts (%)		
				Cutaneous	Ocular	Unknown	M1a	M1b	M1c
RR	Overall	9*		8/9 (89)	1/9 (11)	0	5/9 (56)	2/9 (22)	3/9 (33)
	CR	4/9	14+ – 30	3/4 (75)	1/4 (25)	0	1/4 (25)	1/4 (25)	2/4 (50)
	PR*	5/9	3 – 37+	5/5 (100)	0	0	3/5 (60)	1/5 (20)	1/5 (20)
SD		14	1.5 – 21	7/14 (50)	4/14 (29)	2/14 (14)	5/14 (21)	5/14 (21)	7/14 (50)
PD		12		8/12 (67)	3/12 (25)	0	1/12 (8)	1/12 (8)	9/12 (75)
No response data		2	2 (1cutaneous, M1c and 1unknown, M1c) unknown response						

* One additional responder was not confirmed per RECIST, had PD and rendered surgically NED with no progression at 16+ months. This patient has been designated SD.

PR: partial response; CR: complete response; SD: stable disease; NED: no evidence of disease.

Table 12. Durability of responses and stable disease (3 month duration or longer).

Responders

Primary	Classification	Duration (Months)	Comment
1. Cutaneous	M1a	37+	PR → surgical CR (NED)
2. Cutaneous	M1c	30	CR
3. Ocular	M1c	28+	CR
4. Cutaneous	M1c	20	PR→PD → Surgical NED 4+ months
5. Cutaneous	M1a	18+	CR
6. Cutaneous	M1b	12+	PR (likely CR; residual 4 mm lung nodule)
7. Cutaneous	M1a	6	PR
8. Cutaneous	M1a	6	PR
9. Cutaneous	M1b	14+	CR

Durable Stable Disease (≥3 months)			
1. Unknown	M1a	4	
2. Cutaneous	M1c	9	
3. Ocular	M1c	4.5	
4. Ocular	M1c	13	
5. Cutaneous	M1b	21	
6. Cutaneous	M1b	4	
7. Ocular	M1c	7	
8. Cutaneous	M1b	4.5	
9. Cutaneous	M1a	10.5	
10. Unknown	M1c	4	→ surgical NED for 5 months
11. Cutaneous	M1a	3	Unconfirmed PR →PD → Surgical NED 16+ months
PR: partial response; CR: complete response; SD: stable disease; NED: no evidence of disease			

Table 13. One Year Survival Rate Observed vs Predicted (Korn Model)
As of 2/16/2011

Gender	PS	Visceral Disease	Total	# Alive @ 1 year	Observed Rate	Predicted Rate
Male	0	N	3	2	67%	35%
Male	0	Y	11	9	82%	22%
Male	1	N	3	3	100%	17%
Male	1	Y	6	2	33%	10%
Female	0	N	0	0	---	49%
Female	0	Y	4	2	50%	33%
Female	1	N	3	2	76%	27%
Female	1	Y	7	3	43%	16%

* Predicted rates assume the study was open to patients with brain metastasis

One Year Survival Rate Predicted by Korn Model = **21%**

37 Patients Analyzed
- 23 Alive at one year
-14 Dead at one year

Observed 1 Year Survival Rate = **62%**
95% Confidence Interval = **46% - 78%**
One tailed hypothesis test: observed rate better than predicted (21%) -> p <.0001

Korn, et,al, JCO Feb 1, 2008

Table 14. Summary of the frequency of observed/reported irAEs across different studies testing anti-CTLA4 monoclonal antibody therapy				
Study Agent, dose		**Total (%)**	**Grade 3/4/5 (%)**	**Comment**
Phase II CA184-022, IDB Ipilimumab, 3 mg/kg		65	7	No grade 5
Phase II CA184-022, IDB Ipilimumab, 10 mg/kg		70	25	No grade 5
Hodi, NEJM, 2010, PhIII Ipilimumab, 3 mg/kg		61	16	
Studies (CA184-008, 022, 004, or 007), N=325, IDB Ipilimumab, 10 mg/kg		72.3	25.2	
Tarhini, ASCO 2011, AACR 2012 (preliminary data); neoadjuvant Ipilimumab, 10 mg/kg		80	30	No grade 4 or 5
Tarhini, JCO 2011 (N=37) Treme 15 mg/kg + HDI		65	24	No grade 5
	Diarrhea/Colitis	57.0	10.7	1 grade 4
	Hyper/pothyroidism	5.4	0	
	Hypogonadism	2.7	0	
	Hepatitis-Increased AST/ALT/AP/GGT	21.6	10.7	1 grade 4 (GGT)
	Skin rash	62.0	11.0	

1.7 Study Rationale

Patients with advanced metastatic melanoma derive limited survival benefit from currently approved therapeutic options. There is an urgent and unmet need to improve the clinical outcomes of this patient population. Ipilimumab is active in patients with advanced stage melanoma, with an overall survival benefit, durable objective responses and important disease control rates reported mainly across 2 dose levels (3 mg/kg and 10 mg/kg). However, response rates continue to be modest and appear to benefit only a subgroup a patients. Our data from the phase II study combining the anti-CTLA4 monoclonal antibody tremelimumab and HDI have shown the combination to be safe and with promising efficacy results when compared to reported single agent activity of tremelimumab in phase II and III studies and phase II data of IFN-α in metastatic melanoma.(8, 45) Clinically, both IFN-α and ipilimumab have been demonstrated to have significant clinical activity in melanoma, and activity that appears to be associated with the induction of autoimmunity. This autoimmunity is correlated with clinical benefits and a sign of altered immunologic tolerance.(46-60)

Immunologically, both have been demonstrated to up-regulate the pro-inflammatory cytokine response (Th1 polarization) in patients with melanoma,(19, 61) and to be associated with increased T-cell and dendritic cell (DC) infiltration in tumor in clinical responders.(20, 62, 63) Moreover, the impact of IFNα on DCs is well established, affecting almost all stages of myeloid DC generation,

maturation, differentiation and function (11). In addition, in their immature state, IFN-treated DCs induce a 'polarized' T_{h1} cytokine microenvironment (12). Similar to myeloid DCs, IFNs polarize lymphocytes toward a pro-inflammatory T_{h1} phenotype (13-15). In the cytotoxic T cell compartment, type I IFNs induce potent antitumor cell-mediated cytotoxicity (16), and promote natural killer (NK) cell-mediated proliferation and cytotoxicity (17). This Th1 shift in immunity induced by IFN-α may, however, still be countered by other mechanisms (e.g. CTLA-4) explaining more limited activity observed with IFN-α as monotherapy in metastatic melanoma. Combination with CTLA-4 blockade may, however, alter this balance by downregulating the CTLA4 suppressive regulatory elements and possibly releasing inhibitory influences on activated CD25-expressing CD4 and CD8 effector cells, increasing the antitumor response.

We hypothesize that this combination of ipilimumab and HDI will prove superior to single agent ipilimumab in terms of efficacy and with acceptable toxicity as has been demonstrated with the tremelimumab-HDI combination.

1.7.1 Rationale for evaluating 3 mg/kg and 10 mg/kg dose levels of ipilimumab

Some data suggest a dose dependant effect of ipilimumab from 0.3 mg/kg to 10 mg/kg (CA184-022, a randomized phase II trial of ipilimumab at 0.3 mg/kg, 3 mg/kg and 10 mg/kg), where 10 mg/kg appears to have the greatest efficacy. However the 10 mg/kg ipilimumab dose level also appears to have the greatest frequency of Grade 3-4 adverse events based on CA 184-022, and thus a different safety/efficacy profile compared to 3 mg/kg is possible.(64) In addition, the magnitude of survival benefit for ipilimumab 10 mg/kg given with dacarbazine in untreated melanoma (CA 184-024) was comparable to the magnitude of survival benefit for ipilimumab 3 mg/kg given with vaccine in pretreated melanoma by cross-study comparison (CA184-024: HR 0.72 ($p = 0.0009$), median OS 11.2 vs. 9.1 months; MDX010-20: HR 0.68 ($p < 0.0001$), median OS 6.4 vs. 10.0 months). Given that the risk/benefit ratio may differ at the 3 mg/kg and 10 mg/kg dose levels, there is increasing need to further understand the safety/efficacy profile of both 3 mg/kg and 10 mg/kg dosages of ipilimumab in the treatment of melanoma. The following points are relevant to the consideration of testing both 3mg/kg and 10 mg/kg dose levels of ipilimumab in this study:

- The CA184-022 trial in advanced inoperable melanoma patients suggested a dose-dependent effect of ipilimumab with the highest activity observed in the 10 m/kg dose group (BORR 11.1%, 4.2% and 0% for the 10, 3, and 0.3 mg/kg dose groups, respectively).
- In addition, the CA184-022 trial suggested that the frequency of grade 3-4 irAEs was different between the 3 mg/kg and 10 mg/kg ipilimumab doses.
- Immunologically, IFN-α is known to mount a potent pro-inflammatory (Th1 polarized) immune response that may be suppressed by host immune suppressor elements where CTLA4 plays a significant role. Blocking CTLA-4 may release host inhibition of antitumor immunity but it is not known whether a higher dose of ipilimumab is needed for this additive or potentially

synergistic effect. On the other hand, pharmacokinetically, data from CA 184-022 suggest that 10 mg/kg may be the optimal dose where the C_{minSS} (minimum plasma concentration at steady-state) of 20 μg/ml ipilimumab needed to fully abrogate binding of CTLA-4 to B7.1 & B7.2 (near complete receptor saturation) is exceeded in 95% patients at 10 mg/kg versus 30% patients at 3 mg/kg.(64) That study also suggested potentially greater efficacy, but at the expense of potentially greater toxicity.

- The magnitude of survival benefit for ipilimumab 10 mg/kg given with dacarbazine in untreated melanoma (CA 184-024) was similar to the magnitude of survival benefit for ipilimumab 3 mg/kg given with vaccine in pretreated melanoma by cross-study comparison (CA184-024: HR 0.72 ($p = 0.0009$), median OS 11.2 vs. 9.1 months; MDX010-20: HR 0.68 ($p < 0.0001$), median OS 6.4 vs. 10.0 months). Therefore, an evaluation of a more optimal safety/efficacy ratio by testing both dose levels is important.
- We therefore, propose a randomized phase II trial to test the combination of ipilimumab (recently approved by the FDA for metastatic melanoma) at both 3 mg/kg and 10 mg/kg dose levels alone or in combination with IFN-α.

2. Objectives

2.1 Primary Endpoints

2.1.1 Test the hypothesis that the combination of ipilimumab and HDI will improve PFS of patients with advanced metastatic melanoma as compared to ipilimumab alone (across ipilimumab treatment status).

2.2 Secondary Endpoints

2.2.1 Test the hypothesis that the combination of ipilimumab and HDI will prove to be safe and tolerable.

Adverse events will be assessed across all treated cases and specifically comparing predefined **regimen limiting serious adverse events (RLE)** in patients without HDI versus with HDI (at the 2 ipilimumab dose levels and across ipilimumab treatment status). Also, by comparing the RLE rate with ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg (across HDI treatment status).

Within the constraints of the sample size, attempt to test the hypotheses that (1) ipilimumab 10mg/kg will lead to improved PFS in comparison to ipilimumab 3mg/kg (across HDI treatment status); (2) the combination of ipilimumab and HDI will improve OS of patients with advanced metastatic melanoma as compared to ipilimumab alone (across ipilimumab treatment status) and (3) ipilimumab 10mg/kg will lead to improved OS in comparison to ipilimumab 3mg/kg (across HDI treatment status)."

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 registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Patients must have unresectable stage III or stage IV melanoma, either initial presentation or recurrent, that is of cutaneous origin or unknown primary origin and that is histologically diagnosed.

_____ 3.1.3 No more than one prior systemic therapeutic regimen for unresectable stage III or stage IV melanoma. This includes chemotherapy, biologic therapy, biochemotherapy, or investigational treatment. This does not include any therapies given in the adjuvant setting. However, patients are excluded if they have a history of prior treatment for melanoma (either adjuvant or metastatic disease) with ipilimumab or other CTLA-4 inhibitor, or prior interferon-α treatment for metastatic disease (history of adjuvant interferon-α is allowed). There should be a 4-week washout period between last treatment administration and initiation of study therapy.

Rev. 5/14

_____ 3.1.4 Patients must have ECOG performance status of 0-1.

_____ 3.1.5 Patients must not have other significant medical, surgical, or psychiatric conditions or require any medication or treatment that in the opinion of the investigator may interfere with compliance, make the administration of Ipilimumab or HDI hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea. Patients must not have an active infection requiring current treatment with parenteral antibiotics.

_____ 3.1.6 Patients must not have a history of inflammatory bowel disease or diverticulitis (history of diverticulosis is allowed).

_____ 3.1.7 Patients who have other current malignancies are not eligible. Patients with other malignancies are eligible if they have been

continuously disease free for > 5 years prior to the time of randomization. One exception are patients treated with a curative intent and are continuously disease free for > 3 years. These patients would be considered eligible.

Patients with prior history at any time of any in situ cancer, lobular carcinoma of the breast in situ, cervical cancer in situ, atypical melanocytic hyperplasia or Clark I melanoma in situ are eligible.

Patients with prior history of basal or squamous skin cancer are eligible.

_____ 3.1.8 Patients must not have autoimmune disorders or conditions of immunosuppression that require current ongoing treatment with systemic corticosteroids (or other systemic immunosuppressants), including oral steroids (e.g., prednisone, dexamethasone) or continuous use of topical steroid creams or ointments or ophthalmologic steroids. A history of occasional (but not continuous) use of steroid inhalers is allowed. Replacement doses of steroids for patients with adrenal insufficiency are allowed. Patients who discontinue use of these classes of medication for at least 2 weeks prior to randomization are eligible if, in the judgment of the treating physician investigator, the patient is not likely to require resumption of treatment with these classes of drugs during the study.

Exclusion from this study also includes patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis); other CNS autoimmune disease (e.g., poliomyelitis, Multiple sclerosis).

Patients with autoimmune hypothyroid disease or type I diabetes on replacement treatment are eligible.

_____ 3.1.9 Due to the possible effect of treatment with ipilimumab on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g, standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) within 4 weeks prior to randomization.

_____ 3.1.10 Women must not be pregnant or breast-feeding due to the unknown effects of ipilimumab and the combination with HDI on conception and the fetus. All females of childbearing potential must have a blood test or urine study during screening to rule out pregnancy. Please see Section 7 for required pregnancy testing prior to and during treatment.

Female? ____ (Yes or No) Date of blood test or urine study: _____

NOTE: A woman of childbearing potential (WOCBP) 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).

For the purposes of this study, post-menopause is defined as:

- Amenorrhea ≥ 24 consecutive months without another cause, or
- For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥ 35 mIU/mL.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

Men of fathering potential and WOCBP must be using an adequate method of contraception or must abstain from sexual intercourse to avoid conception/pregnancy throughout the study and for up to 26 weeks after the last dose of ipilimumab or HDI in such a manner that the risk of pregnancy is minimized. Men or WOCBP who are unwilling or unable to strictly follow this requirement are not eligible.

_____ 3.1.11 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 ≥ 3000/uL
- ANC ≥ 1500/uL
- Platelets ≥ 100 x 10^3/uL
- Hemoglobin ≥10 g/dL
- Serum creatinine ≤ 1.8 mg/dl
- AST/ALT ≤ 2.5 x ULN for patients with liver metastases and ≤ 2.0 x ULN for patients without liver metastases.
- Serum bilirubin < 2 x ULN for patients with liver metastases and ≤ 1.5 x ULN for patients without liver metastases, (except patients with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL)

_____ 3.1.12 No active or chronic infection with HIV, hepatitis B, or hepatitis C due to the unknown effects of ipilimumab or the combination with HDI.

_____ 3.1.13 Patients must be free of brain metastasis by contrast-enhanced CT/MRI scans within 4 weeks prior to enrollment. If known to have prior brain metastases, must not have evidence of active brain disease after definitive therapy (surgery, radiation therapy or stereotactic radiosurgery) on two successive MRI evaluations at least 3 months apart (one of which is ≤ 4 weeks prior to starting the study drugs).

_____ 3.1.14 All sites of disease must be evaluated within 4 weeks prior to randomization. Patients must have measurable disease as defined by RECIST v1.1 (see Section 6)

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration Procedures

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Rev. 5/14

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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for E3611 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

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**

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log in to http://www.ctsu.org and click on the Regulatory tab to access the RSS web page. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com.

Rev. 5/14

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.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. 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. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

- 4.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.2.2 Investigator's name (NCI number)
- 4.2.3 Cooperative Group Credit
- 4.2.4 Credit Investigator
- 4.2.5 Protocol specific contact information

4.3 Patient Identification

- 4.3.1 Patient's initials (first and last)
- 4.3.2 Patient's Hospital ID and/or Social Security number
- 4.3.3 Patient demographics
  - 4.3.3.1 Gender
  - 4.3.3.2 Birth date
  - 4.3.3.3 Race
  - 4.3.3.4 Ethnicity
  - 4.3.3.5 Nine-digit ZIP code
  - 4.3.3.6 Method of payment
  - 4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Stratification Factors

Stage: III/M1a, M1b, M1c

4.6 Additional Requirements

- 4.6.1 Patients must provide a signed and dated, written informed consent form.
- 4.6.2 Pathological tissue materials are to be submitted as indicated in Section 10 for central review (mandatory) and for future laboratory studies (per patient consent).

4.6.3 Blood samples are to be submitted per patient consent as indicated in Section 11. for future markers related to this study.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E3611 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

Rev. 5/15

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

4.6.4 Data collection for this study will be done exclusively in Medidata Rave. Prior to beginning data entry in Rave, study staff must be registered in Medidata and complete the required training modules. Study staff will receive an invitation to join the study in Rave after evidence of IRB approval is submitted to RSS.

4.6.5 Additional Registration Training Requirement

Mandatory Investigator Training Course

ECOG-ACRIN has developed a training course to provide additional information to enrolling investigators on the toxicity profile of ipilimumab. Each investigator is required to review the slide deck titled: **Ipilimumab Immune Related Adverse Events: Summary and Recommended Management**, prior to their first patient enrollment by accessing the following URL:

Rev. 5/14

http://coccg.mindflash.com/PublicCoursePage.aspx?CourseId=555542873

Patient enrollments will be blocked via the OPEN system if the enrolling investigator **has not** completed the required training. If your site has a patient waiting and the enrolling INV completed the training after the hours of 9am – 5:30pm ET Monday through Friday, please email the ECOG Ipi Education Team at ECOGIpi@ecogchair.org for after hours assistance.

Rev. 5/14

NOTE: If enrolling investigator has already taken the mandatory training course for E1608 or E1609, the course does not need to be repeated for this study.

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 E3611 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

Patients will be randomized to either Arm A (ipilimumab 10 mg/kg + HDI), Arm B (ipilimumab 10 mg/kg alone), Arm C (ipilimumab 3 mg/kg + HDI) or Arm D (ipilimumab 3 mg/kg alone).

Patients must receive their first induction dose within 7 days of randomization.

Use actual weight when calculating the dose.

5.1.1 **ARM A** (ipilimumab 10 mg/kg + HDI)

Induction Phase

- Ipilimumab10 mg/kg I.V. infusion every 3 weeks for 4 doses
- Interferon Alfa-2b, 20 MU/m²/day I.V. x 5 consecutive days out of 7 (e.g., M-F) every week for 4 weeks, followed by10 MU/m²/day subcutaneous every other day (e.g., M,W,F) 3 times each week for 8 weeks

Maintenance Phase

- Ipilimumab10 mg/kg I.V. infusion every 12 weeks, beginning at week 24, for a maximum of 4 doses (wk 24, 36, 48, 60)
- Interferon Alfa-2b10 MU/m²/day subcutaneous every other day (e.g., M,W,F) 3 times each week for 48 weeks

5.1.2 **ARM B** (ipilimumab 10 mg/kg alone)

Induction Phase

- Ipilimumab10 mg/kg I.V. infusion every 3 weeks for 4 doses

Maintenance Phase

- Ipilimumab10 mg/kg I.V. infusion every 12 weeks, beginning at week 24, for a maximum of 4 doses (wk 24, 36, 48, 60)

5.1.3 **Arm C** (ipilimumab 3 mg/kg + HDI)

Induction Phase

- Ipilimumab 3 mg/kg I.V. infusion every 3 weeks for 4 doses
- Interferon Alfa-2b, 20 MU/m²/day I.V. x 5 consecutive days out of 7 (e.g., M-F) every week for 4 weeks, followed by10 MU/m²/day subcutaneous every other day (e.g., M,W,F) 3 times each week for 8 weeks

Maintenance Phase

- Ipilimumab3 mg/kg I.V. infusion every 12 weeks, beginning at week 24, for a maximum of 4 doses (wk 24, 36, 48, 60)
- Interferon Alfa-2b10 MU/m²/day subcutaneous every other day (e.g., M,W,F) 3 times each week for 48 weeks

5.1.4 **Arm D** (ipilimumab 3 mg/kg alone)

Induction Phase

- Ipilimumab 3 mg/kg I.V. infusion every 3 weeks for 4 doses

Maintenance Phase

- Ipilimumab 3 mg/kg I.V. infusion every 12 weeks, beginning at week 24, for a maximum of 4 doses (wk 24, 36, 48, 60)

5.1.5 Ipilimumab Dose Calculations:

The total dose must be calculated using the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion). Dose delays are allowed as per the dosing criteria described later in this section. Infusions should be given over 90 minutes (not bolus or IV push).

Calculate **Total Dose** as follows:

Patient body weight in kg x [10 mg or 3 mg/kg] = total dose in mg

Calculate **Total Infusion Volume** as follows:

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

Calculate **Rate of Infusion** as follows:

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

For example, a patient on Arm A (ipilimumab 10 mg/kg) weighing 114 kg (250 lb) would be administered 1140 mg of ipilimumab (114 kg x 10 mg/kg = 1140 mg) with an infusion volume of 228 mL (1140 mg ÷ 5 mg/mL = 228 mL) at a rate of approximately 2.5 mL/min (228 mL ÷ 90 minutes) in 90 minutes.

5.1.6 Interferon Alfa - 2b Dose Calculations and Special Considerations:

Induction Phase: Interferon Alfa - 2b, 20 MU/m²/day (rounded to the nearest 1.0 million unit) administered I.V. x 5 consecutive days out of 7 (e.g., M-F) every week x 4 weeks. Then, 10 MU/m²/day (rounded to the nearest 1.0 million unit) subcutaneous every other day (e.g., M,W,F) three times each week x 8 weeks.

Maintenance Phase: Interferon Alfa - 2b, 10 MU/m²/day (rounded to the nearest 1.0 million unit) **subcutaneous** every other day (e.g., M,W,F) three times each week x 48 weeks.

Days 2-5 of interferon (IFN) Alfa - 2b administration for weeks 1-4 may be administered at an institution other than the registering institution provided that the registering physician still retains primary oversight responsibility for the patient's treatment. **Day 1 of each of the first 4 weeks** should be administered at the registering institution. Documentation concerning all drugs administered, side effects and tests performed must be forwarded to the registering institution. The registering institution must document any care given at an outside institution.

Self Administration of Subcutaneous Doses: Patients who are deemed competent to self administer the subcutaneous maintenance

doses of IFN Alfa - 2b may do so following the first 4 weeks of treatment. Interferon Alfa-2b should be prescribed in 10 million unit vials (other standard vial strengths are acceptable) with instructions to reconstitute with 1 ml of diluent to reach a final concentration of 10:1. See Appendix VIII for directions and patient IFN information guide. Patients must complete the E3611 Patient Diary -Interferon (Appendix III).

Rev. 5/14

NOTE: Patients randomized to the combination arms (Arm A or Arm C), the protocol does not mandate a specific sequence for the ipilimumab or IFN Alfa intravenous infusions on days when both of these agents are given. One suggested sequence is as follows:

- Start with the ipilimumab infusion given over 90 minutes.
- While the patient is in the 60 minutes observation period that follows the completion of the ipilimumab infusion, provide 500 ml normal saline intravenous hydration prior to IFN Alfa.
- This is followed by IFN Alfa intravenous infusion over 20 minutes.

Rev. 5/14

5.2 Adverse Event Reporting Requirements

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 for timelier 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

Rev. 5/14

- **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.

Rev. 5/15

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

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

Rev. 5/14

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

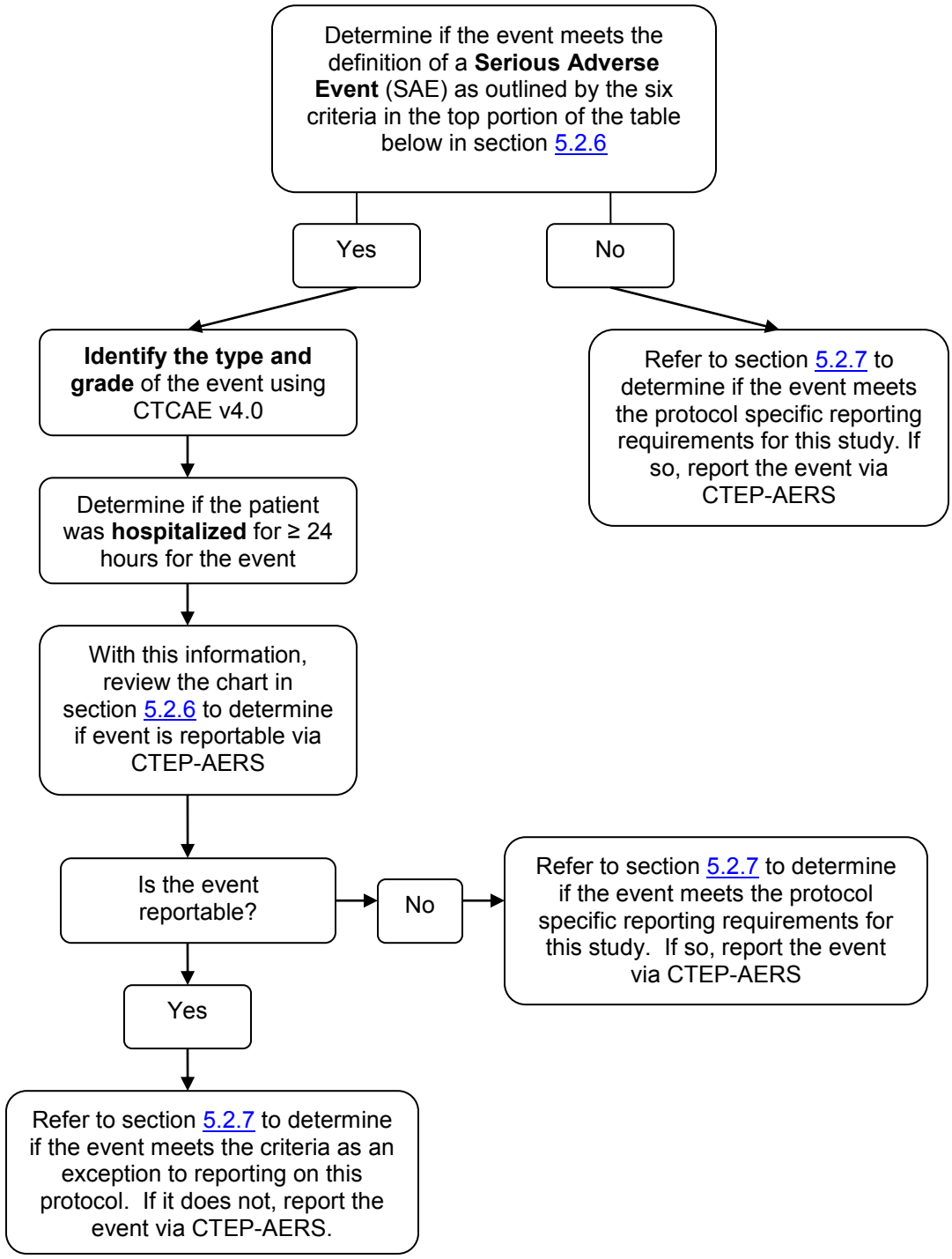
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- 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 E3611 and outline the specific expedited adverse event reporting requirements for study E3611.

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).



Rev. 5/14

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, B, C, and D on protocol E3611

Investigational Agent: Ipilimumab Commercial Agent: Interferon Alfa-2b

Rev. 5/14

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

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 E3611

Additional Instructions:

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 Medical Help Desk at 301-897-7497 or aemd@tech-res.com. This will need to be discussed on a case by case basis.

E3611 specific expedited reporting requirements:

Rev. 5/14

- Immune Related Adverse Events: Any grade 2 or higher immune related adverse event (see section 5.4.1.3 and 5.4.1.4 for definitions), excluding grade 2 or 3 skin reactions, must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected. Please submit any supporting data as well (ie: autoimmune serology tests or biopsy reports).
- Bowel Perforation: Any grade 3 or higher bowel perforation must be reported via CTEP-AERS within 10 calendar days of learning of the event.
- Pregnancy

  Rev. 5/14

  Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Ipilimumab or Interferon Alfa, or within 28 days of the subject's last dose of Ipilimumab or Interferon Alfa, 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 XVII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

E3611 specific expedited reporting exceptions:

Rev. 5/15

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.

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 Second Primary Cancer Reporting Requirements

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 within 14 days in Medidata Rave.
  2. Upload a copy of the pathology reports 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 secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form within 14 days in Medidata Rave.
  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.

Rev. 3/16

5.3 Comprehensive Adverse Events and Potential Risks List

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).

Rev. 5/15

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

Rev. 10/14

Version 2.7, June 28, 2015[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 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]	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypopituitarism/hypophysitis)[2]		
	Endocrine disorders - Other (testosterone deficiency)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<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)***
	Infusion related reaction		
		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)	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (aseptic meningitis)[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
	Facial nerve disorder		
	Headache		
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]		
	Nervous system disorders - Other (myasthenia gravis)[2]		
	Trigeminal nerve disorder		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous 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]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[5]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

[6]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[4]; Eye disorders - Other (retinal pigment changes)

GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[5]

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[6]

INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)

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; Peripheral motor neuropathy; Peripheral sensory neuropathy; 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 (MDX-010) 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 Patients Receiving Ipilimumab

5.4.1.1 Dose and Schedule Modifications for Ipilimumab

There will be no dose reductions for ipilimumab. The dose of ipilimumab will either be given or delayed/discontinued. Patients may develop study drug-related toxicities that may require delaying doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs (Appendix X). Details of how to dose study medication in the presence of adverse drug reactions that may or may not be IRAEs are addressed below.

Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be **possibly, probably or definitely related to ipilimumab treatment. The following criteria will be used to determine dosing delay, restarting doses, and whether ipilimumab should be permanently discontinued. For an adverse event, the investigator should review the following criteria in a stepwise manner: First, assess the dose delay criteria and decide whether a scheduled dose should be delayed. If a dose is delayed and does not meet the dosing criteria within the protocol allowed 3-day window, it should be skipped and should not be made up for. The next opportunity to give an ipilimumab dose would be at the next scheduled dose per protocol/study calendar. Second, determine whether the permanent discontinuation criteria apply to the adverse event in question as well.**

NOTE: Due to the possible effect of treatment with ipilimumab on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) 4 weeks before or after any dose of ipilimumab.

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 IRAEs) except for laboratory abnormalities.
- Any ≥ Grade 3 laboratory abnormality.
- Any ≥ Grade 3 skin-related adverse event (including IRAEs) regardless of causality.

5.4.1.1.2 Criteria to resume ipilimumab treatment

For adverse event(s) that do not meet the ipilimumab permanent discontinuation criteria as noted below, restart ipilimumab dosing if/when the dose delaying adverse event(s) resolve(s) to ≤ Grade 1 severity (except for diarrhea, it should return to baseline) or returns to baseline (e.g., for the induction phase, within 3 weeks [+/- 3 days] of initial dose administration):

- If the adverse event has resolved (to < Grade 1 severity or returns to baseline; for diarrhea, it should return to baseline), restart ipilimumab dosing at the scheduled time point per protocol.
- If the adverse event has not resolved in the protocol specified dosing window (e.g., for the induction phase 3 weeks [+/- 3 days]), the scheduled dose will be omitted.

Please note that for each scheduled dose there is a [+/- 3 days] window within which a scheduled dose may still be given if the dose delaying AE(s) has resolved to ≤ grade 1 (for diarrhea, it should return to baseline before re-dosing).

For patients with grade 2 diarrhea who meet the criteria for resuming dosing with ipilimumab after resolution to baseline should have a colonoscopy (with or without biopsy) to confirm the resolution of the inflammation before ipilimumab may be resumed.

5.4.1.1.3 Criteria for permanent discontinuation of ipilimumab for Related Adverse Events

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

- 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 for this adverse event, 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 under "Exceptions to Permanent Discontinuation" (Section 5.4.1.1.4).
- Any ≥ Grade 4 laboratory abnormalities, except AST, ALT, or Total Bilirubin:
  - AST or ALT > 8 x ULN.
  - Total Bilirubin > 5 x ULN.

NOTE: An exception to permanent discontinuation of ipilimumab is made for laboratory abnormalities that are rapidly reversible, not life threatening, do not reflect underlying organ system dysfunction, and are not related to ipilimumab, such as transient elevations of uric acid, hypocalcaemia, hypophosphatemia.

- Any other ≥ Grade 4 adverse event.
- 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.
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality.
- Any ≥ Grade 3 treatment related sensory neurologic toxicity.
- Patients who require high dose steroids, other immune suppressants or anti-TNF drug therapy for the management of immune related adverse events as described in the Toxicity Management Guidelines/Algorithms should have

ipilimumab permanently discontinued. Treatment with oral budesonide or moderate dose steroids for grade 2 colitis or grade 2 or lower skin rash or higher dose IV steroids for grade 3 skin rash are criteria for ipilimumab dose delay but not permanent discontinuation.

5.4.1.1.4 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 and management.
- 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.

5.4.1.1.5 Differentiating the primary attribution of a certain adverse event and implications on holding a dose and permanent discontinuation.

NOTE: An attempt should be made to differentiate the primary attribution of a certain adverse

event to ipilimumab versus IFN-α before a decision on permanent discontinuation is made. In general, most of IFN- α related AEs, especially laboratory abnormalities, rapidly improve with holding dosing and supportive measures. On the other hand, ipilimumab related immune mediated adverse events that are persistent or serious require intervention with corticosteroids or other immune suppressants.

Adverse events that are related to the combination regimen and meet the thresholds for dose holding or delay per protocol criteria should lead to holding/delaying both agents until resolution to the protocol required criteria for resumption. Decisions on whether to permanently discontinue one or both agents should be made carefully and independently based on the attributions to one agent or the other. If one agent was discontinued based on a specific related adverse event, the other agent may continue to be dosed if it does not meet the protocol permanent discontinuation criteria for the specific adverse event or if the adverse event is determined to be unlikely related. Both agents may be discontinued at the discretion of the treating physician investigator if felt to be in the best interest of the patient to avoid recurrence or development of serious adverse events.

5.4.1.2 Supportive care considerations for ipilimumab administration

5.4.1.2.1 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, pruritus, 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 pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the ipilimumab infusion at the initial planned rate.
  - Diphenhydramine 25-50 mg I.V. 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 pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
  - Interrupt ipilimumab.
  - Administer diphenhydramine 50 mg I.V.
  - 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 solumedrol 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 pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.4.1.2.2 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.

5.4.1.3 Immune-Related Adverse Events (irAEs): Definition, Monitoring, and Treatment

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 drug-related, presumptive autoimmune events, now termed irAEs, noted in previous ipilimumab studies.

For the purposes of this study, an irAE is defined as an AE of unknown etiology associated with ipilimumab 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.

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. See Appendix XI for suggested work-up and treatment of irAEs.

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.

Corticosteroid replacement therapy is not allowed except for patients who develop endocrinopathies during this study that require corticosteroid replacement therapy (such as hydrocortisone) at stable doses.

5.4.1.4 Suggested evaluation and treatment for Immune Related Adverse Events (irAEs) associated with ipilimumab

NOTE: This information has been summarized from the Ipilimumab Investigator Brochure (IB). Please refer to the current version of the IB for more details on the Suggested Work-up and Treatment for irAEs and Management Algorithms. Although these are suggested guidelines that take into consideration potential variations that may be required based on a specific clinical situation, these guidelines are strongly recommended.

Management algorithms for the early detection and treatment of ipilimumab associated toxicities are provided in Appendices Appendix XII-Appendix XVI.

5.4.1.4.1 Immune-mediated Enterocolitis

Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Subjects should be advised to inform the investigator if any diarrhea occurs, even if it is mild. An algorithm for managing subjects with diarrhea or suspected colitis is provided in Appendix XII and the IB. It is suggested that prednisone (for oral administration) or solumedrol (for IV administration) be the corticosteroids of choice in the treatment of colitis.

Corticosteroid therapy (e.g., 1 to 2 mg/kg/day of prednisone po or solumedrol I.V. or equivalent) is strongly recommended for ipilimumab related ≥ Grade 3 diarrhea/colitis. Upon improvement to Grade 1 or less, initiate corticosteroid taper

and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Subjects with ipilimumab related Grade 2 diarrhea/colitis may be initially treated conservatively, but should be immediately switched to corticosteroids if symptoms persist for more than one week or worsen. For severe or persistent symptoms, prednisone (e.g., 0.5 mg/kg/day) or equivalent may be required to control symptoms. Lower doses of prednisone may be considered for less severe cases of colitis.

If the diarrhea is prolonged or severe or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count; or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy of 3 to 5 specimens for standard paraffin block be performed. All subjects with confirmed colitis should also have an ophthalmologic examination, and a slit-lamp exam should be considered at the discretion of the treating physician investigator, to rule out uveitis. Also consider testing for stool calprotectin and stool WBCs as outlined in Appendix XII Negative stool testing for calprotectin or WBCs does not rule out autoimmune colitis.

Infrequently, subjects will appear refractory to corticosteroids or will flare following taper of corticosteroids. In these subjects, unless contraindicated (i.e., sepsis and other serious infections, or perforation), a single dose of infliximab at 5 mg/kg may provide benefit. Infliximab 5 mg/kg may be repeated 2 weeks later if clinically indicated.

5.4.1.4.2 Immune-mediated Hepatitis

Liver function tests should always be performed and reviewed prior to administration of all ipilimumab doses. In addition, subjects presenting with right upper quadrant abdominal pain, unexplained nausea, or vomiting should

have LFTs performed immediately and reviewed before administering the next dose of study drug. A Hepatotoxicity Management Algorithm is provided in Appendix XIII and the current IB.

LFTs ≥ Grade 2 (for subjects with normal baseline LFT) or LFT ≥ 2 times baseline values (for subjects with baseline LFT of Grade 1 or 2) should prompt treating physicians to: (1) increase frequency of monitoring LFTs to at least every 3 days until LFT have stabilized or improved; (2) investigate to rule out non-irAE etiologies; and (3) initiate an autoimmunity evaluation. Disease progression, other malignancies, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile ducts should be considered to rule out neoplastic or other non-irAE-related causes for the increased LFTs. An ANA, perinuclear anti-neutrophil cytoplasmic antibody (pANCA), and anti-smooth muscle antibody test should be performed if an autoimmune etiology is considered. Consultation with a hepatologist is appropriate for a suspected liver IRAE and a biopsy should be considered.

For hepatic transaminases > 5 times the upper limit of normal (ULN) or total bilirubin is > 3 times the upper limit of normal: (1)ipilimumab dosing should be held according to the dose modification guidelines, (2) LFTs should be repeated every 24 hours until stabilization or improvement; and (3) therapeutic intervention with high dose corticosteroids should be strongly considered (e.g., prednisone PO or methylprednisolone I.V. 1-2 mg/kg once or twice daily or equivalent). If symptoms or LFT elevations are controlled, the corticosteroid dose should be gradually tapered over a period of at least 1 month. Flare in LFTs during this taper may be treated with an increase in the dose of steroid and a slower taper. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have

persistent severe hepatitis despite high-dose corticosteroids. The most current experience with immune-related hepatitis has allowed further development of this management algorithm (see flow chart in Appendix XIII and current IB) to include recommendations for treatment.

For hepatic transaminases > 8x the ULN or total bilirubin > 5x the ULN, It is recommended:

a. Admit subject to hospital for evaluation and close monitoring.
b. Stop any further ipilimumab dosing.
c. Start high dose corticosteroids (e.g., 2mg/kg methylprednisolone sodium succinate per day, given IV as a single or divided dose).
d. Check liver laboratory test values (LFTs, T-bilirubin) daily until stable or showing signs of improvement for at least 3 consecutive days.
e. If no decrease in LFTs after 3 days or rebound hepatitis occurs despite treatment with corticosteroids, then add mycophenolate mofetil 1gm BID per institutional guidelines for immunosuppression of liver transplants (supportive treatment as required, including prophylaxis for opportunistic infections per institutional guidelines).
f. If no improvement after 5 to 7 days, consider adding 0.10 to 0.15 mg/kg/day of tacrolimus (trough level 5 20 ng/mL).
g. If target trough level is achieved with tacrolimus but no improvement is observed after 5 to 7 days, consider other immunosuppressant's per institutional guidelines.
h. Continue to check LFTs daily for at least 2 weeks to monitor sustained response to treatment.

5.4.1.4.3 Immune-mediated Pancreas

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may be associated with anti-CTLA-4 monoclonal antibody administration. The differential

diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include serum amylase and lipase tests.

5.4.1.4.4 Immune-mediated Dermatitis

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Any non-protocol drugs that could contribute to a drug reaction should be stopped if possible pending evaluation.

Patients with low-grade ipilimumab-mediated skin toxicity (Grade 1 or 2) may remain on therapy and could be treated with symptomatic therapy (e.g., antihistamines). Low-grade symptoms persisting for 1 to 2 weeks and relapsing should be treated with topical or moderate dose oral corticosteroid therapy (e.g., prednisone 0.5 mg/kg once daily or equivalent).

High-grade (persistent Grade 3 despite moderate dose oral corticosteroid such as prednisone 1 mg/kg once daily or equivalent, or any Grade 4) symptoms require high-dose IV corticosteroid therapy (e.g., prednisone PO or methylprednisolone I.V. at 1-2 mg/kg once or twice per day or equivalent) to control initial symptoms. A skin biopsy should be performed if appropriate. Once rash or pruritis is controlled, the initiation of corticosteroid taper should be based on clinical judgment; however, the corticosteroid dose should be gradually tapered over a period of at least 1 month.

Patients with any high-grade skin related toxicity (Grade 3 regardless of causality) have to skip ipilimumab and may only continue treatment with ipilimumab if the initial symptoms have improved to ≤ Grade 1, while patients with grade 4 skin toxicities (e.g., Stevens-Johnson syndrome, toxic

epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations) have to permanently discontinue ipilimumab.

5.4.1.4.5 Immune-mediated Endocrinopathies

Monitor thyroid function tests, other protocol required tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. Subjects with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, intravenous corticosteroids with mineralocorticoid activity (e.g., methylprednisolone) should be initiated immediately. If the patient's symptoms are suggestive of an endocrinopathy but the patient is not in adrenal crisis, endocrine laboratory results should be evaluated before corticosteroid therapy is initiated.

Endocrine work up should include at least Thyroid stimulating hormone and free T4 levels to determine if thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Radiographic imaging (e.g., MRI) with pituitary cuts should be performed if hypophysitis is suspected. If the pituitary scan and/or endocrine laboratory tests are abnormal and suggestive of pituitary endocrinopathy, a short course of high dose corticosteroids (e.g., dexamethasone 4 mg every 6 hours or equivalent) should be strongly considered in an attempt to treat the presumed pituitary inflammation, but it is currently unknown if this will reverse the pituitary dysfunction.

Abrupt discontinuation of corticosteroids should be avoided due to possible

prolonged adrenal suppression. Once symptoms or laboratory abnormalities are controlled, and overall patient improvement is evident, the initiation of steroid taper should be based on clinical judgment; however the corticosteroid dose should be gradually tapered over a period of at least 1 month. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented, and it is possible that subjects may require life-long hormone replacement.

Please see Appendix XIV and the current IB for the Endocrinopathy Management Algorithm.

5.4.1.4.6 Ocular Manifestations

Ocular inflammation (episcleritis or uveitis), usually in association with colitis, was reported in a few subjects. These conditions responded to topical corticosteroid therapy. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers and retina; visual field testing and an electroretinogram should also be performed. Patients with ipilimumab related uveitis or episcleritis have been treated with topical corticosteroid eye drops. See Section 5.4.1.1.3 for ocular irAEs that may require ipilimumab permanent discontinuation.

5.4.1.4.7 Immune-mediated Neuropathies

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndrome (GBS). Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold ipilimumab dosing in patients with moderate neuropathy (not interfering with daily activities). See

Appendix XV and the current IB for the Neuropathy Management Algorithm.

5.4.1.4.8 Other Immune-mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in reported studies to date: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue ipilimumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.4.2 Patients Receiving Interferon (IFN) Alfa - 2b

Overall, Induction Phase on this protocol includes the first 12 weeks where IFN is given by the I.V. route in the first 4 weeks then S.C. for the next 8 weeks. Maintenance Phase includes S.C. therapy the following 48 weeks. For the purposes of dose modifications for IFN, the 4 weeks of I.V. therapy shall be evaluated separately from the remaining weeks of S.C. IFN therapy. A patient requiring dose modification(s) for IFN in the first month of I.V. therapy will therefore commence month 2 without prejudice, at full IFN S.C. dosage. **Doses missed** during treatment due to toxicity, patient compliance, holiday, etc. should **not** be made up.

Overview

If a patient requires a dose modification (details are listed below), treatment must first be held until AE resolution to ≤ Grade 1 before

IFN resumption. The first modification then requires a 33% reduction of dosage and the second modification requires a 66% reduction of dosage. A patient who requires a third dose modification will have IFN permanently discontinued. Dose re-escalation will not be attempted following resolution of toxicity that required dose interruption or attenuation. The following table summarizes IFN dose modifications.

	Full Treatment	Dose Mod 1	Dose Mod 2	Dose Mod 3
High Dose IFN Alfa - 2b I.V. (Weeks 1-4):	20 MU/m²	13.3 MU/m²	6.6 MU/m²	Off
High Dose IFN Alfa - 2b **Subcutaneous** (Weeks 5+):	10 MU/m²	6.6 MU/m²	3.3 MU/m²	Off

The following are the most common toxicities observed with interferon. Guidelines for HDI Dose Modification and Discontinuation are also provided. These toxicities and their management guidelines are based on experience from previous studies (E1684, E1690, E1694) and the following 2 publications that may also serve as additional resources on the toxicities associated with HDI and their management:

Kirkwood JM, Bender C, Agarwala S, Tarhini A, Shipe-Spotloe J, Smelko B, Donnelly S, Stover L. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. J Clin Oncol. 2002 Sep 1;20(17):3703-18. Review.

Hauschild A, Gogas H, Tarhini A, Middleton MR, Testori A, Dréno B, Kirkwood JM. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer. 2008 Mar 1;112(5):982-94.

NOTE: Dose modifications may be done for toxicities related to HDI therapy even if they don't fit these guidelines if it is determined by the treating physician that it is in the best interest of the patient for safety reasons taking into consideration the overall clinical status of the subject. A note has to be made of such a modification.

- Constitutional Toxicity: Fever, chill, myalgia/arthralgia, fatigue, headache: these constitutional toxicities are observed in the first weeks of treatment. Fatigue may worsen during the course of therapy and require a dose modification. In general, dose modifications are done for grade 3 or 4 toxicities.
- Myelotoxicity: Leukopenia, anemia and thrombocytopenia are observed with acute and chronic interferon therapy. Dose modifications are indicated for grade 4 granulocytopenia and grade 3 thrombocytopenia.
- Hepatotoxicity: Fatal hepatotoxicity has been observed in patients receiving sustained intensive high dosages of interferon, and close attention to the occurrence of hepatocellular enzyme abnormalities is warranted. Grade 3 or greater elevations of

bilirubin, AST or ALT require dosage modification. Isolated elevation in other LFT's should also be examined carefully, preferably in consultation with a hepatology specialist and dose modification should be considered if underlying liver damage is suspected.

- Nephrotoxicity: Acute kidney injury of Grade 1 (CTCAE v.4) that is not rapidly responsive to hydration (PO or IV) is an indication for dose modification and elevations of Grade 2 (not rapidly responsive to hydration) require withdrawal of therapy. Patients should be advised to maintain adequate oral fluid hydration of about 1.5 – 2 liters per day during IFN Alfa - 2b.
- Neurotoxicity, including Neuropsychiatric, Neurosensory, and Neuromotor: Mood alterations and cognitive dysfunction have been reported as toxicities of the interferons, especially in the elderly and those with underlying disorders. Grade 3 or greater Neurotoxicity is a dose modification criterion, and if neuropsychiatric toxicity is encountered this ought to be evaluated by a capable specialist (psychiatrist, and/or clinical psychologist).
- Cardiopulmonary: Cardiac arrhythmia has been reported as a complication of interferon therapy, and the appearance of signs or symptoms of cardiac arrhythmia, or other cardiopulmonary toxicity of Grade 2 dictates dose modification, and resumption of treatment only after normalization and, in general, formal cardiologic evaluation and clearance. Grade 3 toxicity at any time requires withdrawal of therapy.
- Gastrointestinal: Nausea, vomiting, and/or diarrhea are infrequent but well-defined toxicities of interferon, which may abate with supportive care but require dose modification if observed at Grade 3, at any time, or if persistent for more than 2 weeks at Grade 2. Weight loss of Grade 2 is likewise a criterion for dose modification if observed over a period of one month.

Suggested HDI Dose Modification and Discontinuation Guidelines:

Toxicity	1. Threshold for Reduction 2. % Dose Reduction from Starting Dose 3. Threshold for Resumption		
	First Dose Reduction	Second Dose Reduction	Treatment Discontinuation
Autoimmune Reactions			
Hypothyroidism	None	None	Discontinue if thyroid function is unstable with treatment.
Psoriasis	1. ≥ grade 2 skin rash (localized desquamation or other lesions covering <50% of body surface area) 2. 33% 3. Grade 1 (erythema without associated symptoms)	1. ≥ grade 2 skin rash (localized desquamation or other lesions covering <50% of body surface area) 2. 66% 3. Grade 1 (erythema without associated symptoms)	1. ≥ grade 2 skin rash (localized desquamation or other lesions covering <50% of body surface area) 2. Discontinue
Hematologic Toxicity			
Granulocytopenia	1. < 500 cells/mm^3 (Grade 4) 2. 33% 3. ≥1000 cells/mm^3	1. < 500 cells/mm^3 (Grade 4) 2. 66% 3. ≥1000 cells/mm^3	1. < 500 cells/mm^3 (Grade 4) 2. Discontinue
Thrombocytopenia	1. < 50,000 cells/mm^3 (Grade 3) 2. 33% 3. >75,000 cells/mm^3 (Grade 1)	1. < 50,000 cells/mm^3 (Grade 3) 2. 66% 3. >75,000 cells/mm^3 (Grade 1)	1. <50,000 cells/mm^3 (Grade 3) 2. Discontinue
Other			
Anorexia	1. Grade 3 or 4 2. 33% 3. Grade 2	1. Grade 3 or 4 2. 66% 3. Grade 2	1. Grade 3 or 4 2. Discontinue
Cardiotoxicity	1. Grade 2 2. 33% 3. Normalization and, consider formal cardiologic evaluation and clearance	1. Grade 2 2. 66% 3. Normalization and, consider formal cardiologic evaluation and clearance	1. Grade 2 2. Discontinue. 3. Grade 3 toxicity at any time requires withdrawal of therapy

Creatine Kinase (CPK)	1. > 5 times normal (in the absence of a clinical suspicion of rhabdomyolysis) or any elevation and a clinical suspicion of rhabdomyolysis 2. 33% 3. ≤ 2 times normal	1. > 5 times normal (in the absence of a clinical suspicion of rhabdomyolysis) or any elevation and a clinical suspicion of rhabdomyolysis 2. 66% 3. ≤ 2 times normal	1. > 5 times normal 2. Discontinue. 3. Discontinue at any time if diagnosed with rhabdomyolysis.
Depression	1. Grade 3 or 4 2. 33% 3. Grade 1	1. Grade 3 or 4 2. 66% 3. Grade 1	1. Grade 3 or 4 2. Discontinue
Diarrhea	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 33% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 66% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. Discontinue
Fatigue	1. Grade 3 or 4 2. 33% 3. Grade 1	1. Grade 3 or 4 2. 66% 3. Grade 1	1. Grade 3 or 4 2. Discontinue
Flu-like Symptoms-Constitutional Symptoms	1. Grade 3 or 4 2. 33% 3. Grade 1	1. Grade 3 or 4 2. 66% 3. Grade 1	1. Grade 3 or 4 2. Discontinue
Hepatotoxicity (SGPT [ALT] SGPT [AST])	1. > 5 times normal (Grade 3 or 4) 2. 33% 3. Grade 1	1. > 5 times normal (Grade 3 or 4) 2. 66% 3. Grade 1	1. > 5 times normal (Grade 3 or 4) 2. Discontinue
Nausea	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 33% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 66% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. Discontinue
Ocular toxicity	None	None	Discontinue for any ocular toxicity
Renal	1. Grade 1 2. 33% 3. normal	1. Grade 1 2. 66% 3. normal	1. Grade 1 2. Discontinue 3. Elevations of Grade 2 or higher at anytime require withdrawal of therapy
Vomiting	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 33% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. 66% 3. Grade 1	1. Grade 3 or 4 or if persistent for more than 2 weeks at Grade 2 2. Discontinue

Weight loss	1. Grade 2 if observed over a period of one month and is unintentional 2. 33% 3. Continue at the reduced dose if no other limiting adverse events	1. Grade 2 if observed over a period of one month and is unintentional 2. 66% 3. Continue at the reduced dose if no other limiting adverse events	1. Grade 2 is if observed over a period of one month and is unintentional 2. Discontinue.

5.5 Supportive Care and Prohibited Therapies

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

5.5.2 See Section 5.4.1.2 that provides supportive care considerations for ipilimumab administration.

5.5.3 Patients requiring chemotherapy or radiation therapy during the study will be taken off study treatment. Any exceptions must be discussed with the study chair.

5.5.4 Additional Prohibited and Restricted Therapies During the Study.

5.5.4.1 Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease (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 or HDI 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 CTLA-4 inhibitors or agonists
- CD137 agonists, PD-1 inhibitors
- Immunosuppressive agents, unless indicated to manage study therapy induced irAEs
- Chronic systemic corticosteroids, unless indicated to manage study therapy induced irAEs
- 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).

5.5.4.2 Precautions

Caution is advised when considering treatment with high-dose IL-2 in patients who have previously been administered ipilimumab, particularly in patients who

experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable prior to IL-2 administration once the patient is no longer receiving ipilimumab.

5.6 Duration of Therapy

The duration of therapy on all study arms is approximately 60 weeks.

Patients will receive protocol therapy unless:

5.6.1 Melanoma disease progression by protocol criteria: in which case patients will be removed from study treatment. They will, however, continue to be followed for survival. In addition, data on salvage patterns post recurrence will be collected.

5.6.2 Patients will be discontinued from treatment in the event of unacceptable toxicity (see protocol therapy discontinuation criteria in Section 5), pregnancy, change in medical condition or noncompliance with the study protocol that in the opinion of the investigator, necessitates removal of patient from treatment.

5.6.3 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 E3611 Forms Completion Guidelines.

5.6.4 Patient withdraws consent.

5.6.5 Patient experiences unacceptable toxicity.

5.6.6 Prohibited non-protocol therapies are administered.

5.7 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 10 years from the date of registration.

6. Measurement of Effect

6.1 Antitumor Effect – 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 not less than 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.

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).

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

FDG-PET

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

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.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered 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 6 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 lesion(s.

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).

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 ≥ 6 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 6 weeks.

6.2 Definition of Tumor Response Using irRC

The sum of the products of diameters (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.

6.2.1 Definition of Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all index 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 index and all new measurable lesions (ie., 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 ≥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 sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.

6.2.2 Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- irPartial Response (irPR) or irStable Disease (irSD): non-index lesion(s) are not considered in the definition of PR, these terms do not apply.
- irProgressive Disease (irPD): Increases in number or size of non-index 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 index lesions increases by the required amount).

6.2.3 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.

6.2.4 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 (index and nonindex 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 index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index 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 sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Table 11: Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index 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

6.2.5 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.

6.2.6 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 the 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.

Therefore, 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. 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.

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization.
2. Prestudy (screening) CBC (with differential and platelet count) chemistries and other laboratory studies required in Section 3 (Selection of Patients) should be done ≤ 4 weeks before randomization.
3. All required pretreatment laboratory studies should be done as outlined in the study calendars in Sections 7.2 and 7.3.
4. For WOCBP, pregnancy test (b-HCG test; serum or urine, minimum sensitivity 25 IU/L or equivalent units of b-HCG) must be done during screening within four weeks prior to randomization. Following randomization, serum or urine pregnancy test must be done within 72 hours prior to each dose of ipilimumab.

7.2 Arms A and C: Patients Treated with HDI and Ipilimumab at 10 mg/kg (Arm A) or 3 mg/kg (Arm C)

Test/ Assessment	Within 4 weeks (28 days) of rando-mization	Induction Phase[a]							Week 12 ±1 wk	Maintenance Phase[a] Until 12 weeks after last ipilimumab dose (or 6 Weeks after last IFN-α2b dose if ipilimumab was discontinued >12 weeks earlier) or until relapse		End of Study Assessment[n]	Follow Up[m]
		D1 + 3d (wk1)	D8 (wk2)	D15 (wk3)	D22 + 3d (wk4)	D29 (wk5)	D43 ± 3d (wk7)	D64 ± 3d (wk10)		Week 24, 36, 48, 60 ± 1 Week	Every 6 Wks ±1 Week		
Informed Consent	X												
History/Physical/ ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid, immunosuppressant, hormone meds Log	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology labs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry labs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	See Footnote e												
Pregnancy test (b-HCG)[f]	X[f]	X[f]			X[f]		X[f]	X[f]		X[f]			
HIV, HBV, HCV[g]	X												
Immunologic labs[h,a]	See Footnote h												
Hormonal studies[i,a]		X[i]			X[i]		X[i]	X[i]	X[i]	X[i]		X[i]	
ECG	X												
Ophthalmologic examination[j]	X[j]									X[j]			X[j]
Ipilimumab infusion		X			X		X	X		X			
Adverse events assessment[k]		X	X	X	X	X	X	X	X	X	X	X	X

Imaging studies[l]	X[l]								X[l]	X[l]		X[l]
Interferon Diary		X	X	X	X	X	X	X	X	X		
Biological sample submissions	See Section 7.4											

a. All Study procedures, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to administration of ipilimumab dose. Baseline pregnancy exam must be performed within 3 days of beginning ipilimumab dosing and determined to be negative. During the maintenance phase, in addition to the evaluations done on the dosing days every 12 weeks, patients will be seen and evaluated as noted in the study calendar every 6 weeks (-/+ 1 week), starting at week 18. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator. Hormonal studies and immunologic labs are required for monitoring at the specified time points and as clinically indicated. The results of these tests (hormonal studies and immunologic labs) are not required for dosing unless there are clinical indications and/or associated adverse events as described under the Section on Dose and Schedule Modifications for Ipilimumab and the Section on HDI Dose Modification and Discontinuation Guidelines.

b. For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (-/+ 5 minutes) during dosing and 30 - 60 minutes (-/+ 10 minutes) after dosing until vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing, every 30 minutes (-/+ 10 minutes) during dosing, and 1 hour (-/+ 10 minutes) post dosing.

c. Hematology labs to include hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets (direct platelet count), as well as total and differential CBC counts. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

d. Chemistry laboratory analysis includes albumin, amylase, lipase, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. In follow up (after completion of ipilimumab treatment), amylase and lipase will be done only if clinically indicated. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

e. Urinalysis will be done as clinically indicated. Urinalysis tests to include gross examination including specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as clinically indicated, to include WBC/HPF, RBC/HPF and any additional findings.

f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening. Serum or urine pregnancy test must be done within 72 hours prior to each dose of ipilimumab.

g. 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.

h. The following labs are to be done at baseline (within 4 weeks of starting the study drug) and at 12, 24, 42, 60, and 96 weeks, and at melanoma relapse (+/- 2 weeks for all time points except the 96 week time point, a +/- 4 weeks window is allowed). If melanoma relapse occurs before any of these time points, no additional testing needs to be done after the relapse time point: C-reactive protein, Antinuclear antibody (ANA) Screen, Thyroid Stimulating Immunoglobulin (TSI), Antithyroglobulin antibody (ATGAB), Antithyroperoxidase Antibody (ATPOAB), Anticardiolipin Antibody (TOTAL). These labs must be completed even if the patient goes off treatment early for any reason other

than progression. If melanoma progression occurs before any of these time points, no additional testing needs to be done after the relapse time point.

i. Hormonal studies: To be done at the indicated visits and when clinically indicated. These include TSH, free T4, morning ACTH, morning cortisol. For Men: testosterone. For WOCBP: prolactin, LH, FSH, and estradiol that will be done only if a WOCBP is experiencing amenorrhea while on protocol treatment. For days 22 and 64 (-/+ 3 days) only TSH and free T4 are required while others are to be done only if clinically indicated.

j. Ophthalmologic examination will be done at baseline only if clinically indicated. On this study, the last dose of ipilimumab will be at approximately week 60. Ophthalmological examination is strongly recommended to be done at 6 and 18 months (± 4 weeks) after start of treatment, especially in patients who experienced diarrhea or colitis, preferably performed by an ophthalmologist. If melanoma recurrence occurs before these time points, the ophthalmological examination should still be done if clinically indicated. It should also be performed at other time points if clinically indicated.

k. 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 E1609 Adverse Event Forms, covering all time periods specified on the forms.

l. Baseline imaging studies: should be done within 4 weeks prior to randomization. These must include a brain MRI or CT (if MRI is contraindicated or cannot be done) and CT of chest, abdomen and pelvis. A PET-CT scan may be done instead of CT. If for some reason a CT cannot be done, an MRI may be done instead. Imaging of other sites (e.g. neck, lower extremities) should be obtained when clinically indicated. Other imaging studies (e.g., bone scan) may be performed if clinically indicated. During treatment and on follow-up: CT (or MRI if CT cannot be done) chest/abdomen/pelvis will be done every 3 months (-/+ 1 week) for the first year from study entry, every 3 months (-/+ 2 weeks) for the 2nd year, then every 6 months (+/- 4 weeks) for the 3rd, 4th and 5th years from study entry, and annually (+/- 4 weeks) if patient is >5 years from study entry for up to 10 years. A PET-CT is not required, but is acceptable if done. However, if PET-CT was done at baseline, it should also be done on follow up assessments. Brain MRI/CT or other imaging studies may be done as clinically indicated but are not required in the absence of clinical indications.

m. Follow up period will start 12 weeks after the last ipilimumab dose (or 6 weeks after last IFN-a2b dose if ipilimumab was discontinued >12 weeks earlier) for patients who have no disease progression. These patients should be seen at 6 weeks (-/+ 1 week) after the last dose then 12 weeks (-/+ 1 week) after the last dose and later evaluated per the standard ECOG-ACRIN follow-up schedule: Every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. However, patients with ongoing toxicities should be seen more often as clinically indicated. Patients who develop melanoma progression will be followed for survival and for information on salvage patterns. The schedule of clinical follow up for these patients will be at the discretion of the treating physicians and according to established Standard of Care. Adverse Events Assessment on the study will continue for all patients until 90 days after the last study drug administration.

n. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of ipilimumab or interferon, whichever was given last. This is after completion/discontinuation of both regimen agents (ipilimumab and interferon).

7.3 Arms B and D: Patients Treated with Ipilimumab alone at 10 mg/kg (Arm B) or 3 mg/kg (Arm D)

Test/ Assessment	Within 4 weeks (28 days) of randomi-zation	Induction Phase[a]				Week 12 ± 1 week	Maintenance Phase[a] (Until 12 weeks after the last ipilimumab dose or until relapse)		End of Study Assessment[n]	Follow Up[m]
		Day 1± 3 days (Week 1)	Day 22 ± 3 days (Week 4)	Day 43 ± 3 days (Week 7)	Day 64 ± 3 days (Week 10)		Week 24, 36, 48, 60 ± 1 Week	Every 6 Weeks ±1 Week		
Informed Consent	X									
History/Physical/ ECOG PS	X	X	X	X	X	X	X	X	X	X
Weight/Vital Signs[b]	X	X	X	X	X	X	X	X	X	X
Corticosteroid, immunosuppressant, hormone meds Log		X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	
Hematology labs[c]	X	X	X	X	X	X	X	X	X	X
Chemistry labs[d]	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	See Footnote e									
Pregnancy test (b-HCG)[f]	X	X	X	X	X		X			
HIV, HBV, HCV[g]	X									
Immunologic labs[h]	See Footnote h									
Hormonal studies[i]		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]		X[i]	
ECG	X									
Ophthalmologic examination[j]	X[j]						X[j]			X[j]
Ipilimumab infusion		X	X	X	X		X			
Adverse events assessment[k]		X	X	X	X	X	X	X	X	X
Imaging studies[l]	X[l]					X[l]	X[l]			X[l]
Biological sample submissions	See Section 7.4									

Rev. 5/14

a. All Study procedures, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to administration of ipilimumab dose. Baseline pregnancy exam must be performed within 3 days of beginning ipilimumab dosing and determined to be negative. During the maintenance phase, in addition to the evaluations done on the dosing days every 12 weeks, patients will be seen and evaluated as noted in the study calendar every 6 weeks (-/+ 1 week), starting at week 18. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator. Hormonal studies and immunologic labs are required for monitoring at the specified time points and as clinically indicated. The results of these tests (hormonal studies and immunologic labs) are not required for dosing unless there are clinical indications and/or associated adverse events as described under the Section on Dose and Schedule Modifications for Ipilimumab and the Section on HDI Dose Modification and Discontinuation Guidelines.

b. For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (-/+ 5 minutes) during dosing and 30 - 60 minutes (-/+ 10 minutes) after dosing until vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing, every 30 minutes (-/+ 10 minutes) during dosing, and 1 hour post dosing.

c. Hematology labs to include hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets (direct platelet count), as well as total and differential CBC counts. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

d. Chemistry laboratory analysis includes albumin, amylase, lipase, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. In follow up (after completion of ipilimumab treatment), amylase and lipase will be done only if clinically indicated. These labs must be done and reviewed before ipilimumab infusion. These labs are required to be done throughout follow-up regardless if the patient goes off treatment early for anything other than recurrence. Once recurrence occurs, these labs are no longer required to be completed.

e. Urinalysis will be done as clinically indicated. Urinalysis tests to include gross examination including specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as clinically indicated, to include WBC/HPF, RBC/HPF and any additional findings.

f. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening. Serum or urine pregnancy test must be done within 72 hours prior to each dose of ipilimumab.

g. 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.

h. The following labs are to be done at baseline (within 4 weeks of starting the study drug) and at 12, 24, 42, 60, and 96 weeks, and at melanoma relapse (+/- 2 weeks for all time points except the 96 week time point, a +/- 4 weeks window is allowed). If melanoma relapse occurs before any of these time points, no additional testing needs to be done after the relapse time point: C-reactive protein, Antinuclear antibody (ANA) Screen, Thyroid Stimulating Immunoglobulin (TSI), Antithyroglobulin antibody (ATGAB), Antithyroperoxidase Antibody (ATPOAB), Anticardiolipin Antibody (TOTAL). These labs must be completed even if the patient goes off treatment early for any reason other than progression. If melanoma progression occurs before any of these time points, no additional testing needs to be done after the relapse time point.

i. Hormonal studies: To be done at the indicated visits and when clinically indicated. These include TSH, free T4, morning ACTH, morning cortisol. For Men: testosterone. For WOCBP: prolactin, LH, FSH, and estradiol that will be done only if a WOCBP is experiencing amenorrhea while on protocol treatment. For days 22 and 64 (-/+ 3 days) only TSH and free T4 are required while others are to be done only if clinically indicated.

j. Ophthalmologic examination will be done at baseline only if clinically indicated. On this study, the last dose of ipilimumab will be at approximately week 60. Ophthalmological examination is strongly recommended to be done at 6 and 18 months (± 4 weeks) after start of treatment, especially in patients who experience diarrhea or colitis, preferably performed by an ophthalmologist. If melanoma recurrence occurs before these time points, the ophthalmological examination should still be done if clinically indicated. It should also be performed at other time points if clinically indicated.

k. 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 E1609 Adverse Event Forms, covering all time periods specified on the forms.

l. Baseline imaging studies: should be done within 4 weeks prior to randomization. These must include a brain MRI or CT (if MRI is contraindicated or cannot be done) and CT of chest, abdomen and pelvis. A PET-CT scan may be done instead of CT. If for some reason a CT cannot be done, an MRI may be done instead. Imaging of other sites (e.g. neck, lower extremities) should be obtained when clinically indicated. Other imaging studies (e.g., bone scan) may be performed if clinically indicated. During treatment and on follow-up: CT (or MRI if CT cannot be done) chest/abdomen/pelvis will be done every 3 months (-/+ 1 week) for the first year from study entry, every 3 months (-/+ 2 weeks) for the 2nd year, then every 6 months (+/- 4 weeks) for the 3rd, 4th and 5th years from study entry, and yearly (+/- 4 weeks) if patient is >5 years from study entry for up to 10 years. A PET-CT is not required, but is acceptable if done. However, if PET-CT was done at baseline, it should also be done on follow up assessments. Brain MRI/CT or other imaging studies may be done as clinically indicated but are not required in the absence of clinical indications.

m. Follow up period will start 12 weeks after the last ipilimumab dose for patients who have no disease progression. These patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, and later evaluated per the standard ECOG-ACRIN follow-up schedule: Every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. However, patients with ongoing toxicities should be seen more often as clinically indicated. Patients who develop recurrent melanoma will be followed for survival and for information on salvage patterns. The schedule of clinical follow up for these patients will be at the discretion of the treating physicians and according to established Standard of Care. Adverse Events Assessment on the study will continue for all patients until 90 days after the last study drug administration.

n. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of ipilimumab.

Rev. 5/15

7.4 Biological Sample Submissions

1. Submission of pathology samples at baseline for diagnostic review is mandatory in order for the patient to be considered evaluable. See Section 10 (Pathology Review) and Appendix I (Pathology Submission Guidelines).
2. Pathology samples for future laboratory studies should be submitted as outlined in Section 10 per patient consent.
3. Blood samples for future laboratory studies should be submitted as outlined in Section 11 per patient consent.

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) for purposes of monitoring compliance.

NOTE: An informed consent must be signed prior to the submission of any samples, including mandatory diagnostic reviews and future laboratory studies. Blood samples for future use should be submitted only from patients who have given written consent for the use of their samples for these purposes.

Material	Baseline[1]	Day 19 [+ 4 day window] (End Week3 / Start Week4)[10]	After 12 Weeks of Initiating Treatment[2]	At 48 Weeks[2, 3]	Progression/ Relapse
Pathology Samples[6]	X[9]				X[8]
Patient consents "Yes" to "I agree to provide additional blood for research."					
Peripheral Blood Mononuclear Cells (ten 10cc green top heparin tubes)[4,5,7]	X	X	X	X	X[2,3]
Serum (three 10cc red top tubes)[4,5,7]	X	X	X	X	X[2,3]
PAXgene RNA Tube (1)[4,5,7]	X	X	X		
ACD Tube (one 10cc yellow top tube)[4,5,7]	X				

1. Prior to treatment
2. +/- 1 week.
3. If relapse occurs before the 48 week time point, no additional blood samples are required after the relapse blood sample is sent.
4. Kits are being provided for the collection and shipment of the blood samples. Please refer to Section 11.3 for instructions.
5. Please completely fill all blood tubes as full as possible.
6. Submit to ECOG-ACRIN Central Biorepository and Pathology Facility.
7. Submit to ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory.
8. Submit from patients who have consented to future laboratory studies.
9. Mandatory submission for central review.
10. Day 19 (+ 4day window) sample should be obtained before giving the second dose of ipilimumab.

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, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Ipilimumab (NSC 732442) (IND #10200) 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,
Rev. 5/14 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 be used or substituted for the NCI-supplied ipilimumab.

Rev. 5/14 **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
Rev. 5/14 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
Rev. 5/14 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)

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, E3611, 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 specific for the CTLA4 antigen expressed on a subset of activated T cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

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 $\geq$ 2°C and $\leq$ 8°C.

Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 4 mg/mL. Undiluted or 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. 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 B		Process C	
Component	**50 mg/ vial[a]**	**200 mg/ vial[b]**	**50 mg/ vial[a]**	**200 mg/ vial[b]**
Ipilimumab	53.5 mg	213 mg	53.5 mg	213 mg
Sodium Chloride, USP	62.6 mg	249 mg	62.6 mg	249 mg
TRIS-hydrochloride	33.7 mg	134.3 mg	33.7 mg	134.3 mg
Diethylenetriamine pentacetic acid	0.42 mg	1.67 mg	0.42 mg	1.67 mg
Mannitol, USP	107 mg	426 mg	107 mg	426 mg
Polysorbate 80 (plant-derived)	1.07 mg	4.26 mg	1.18 mg	4.69 mg
Sodium Hydroxide	QS to pH 7			
Hydrochloric acid	QS to pH 7			
Water for Injection	QS: 10.7 mL	QS: 42.6 mL	QS: 10.7 mL	QS: 42.6 mL
Nitrogen[c]	Processing agent			

[a] Includes 0.7 overfill

[b] Includes 2.6 mL overfill.

[c] 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 10 mg/kg (Arm A and Arm B) or 3 mg/kg (Arm C and Arm D), administered by IV infusion every three weeks for a total of four doses, until local recurrence or distant progression, unacceptable toxicity or withdrawal of consent.

Maintenance Phase

Ipilimumab 10 mg/kg (Arm A and Arm B) or 3 mg/kg (Arm C and Arm D), administered by IV infusion every 12 weeks (3 months), beginning at Week 24, then at weeks 36, 48, 60, until disease recurrence, unacceptable toxicity or withdrawal of consent for a maximum of 4 maintenance doses.

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

8.1.6.1 Dose Calculations: Calculate **Total Dose** as follows:

Patient body weight in kg x [10 mg or 3 mg/kg] = total dose in mg

Calculate **Total Infusion Volume** as follows:

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

Calculate **Rate of Infusion** as follows:

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

For example, a patient on Arm A weighing 114 kg (250 lb) would be administered 1140 mg of ipilimumab (114 kg x 10 mg/kg = 1140 mg) with an infusion volume of 228 mL

(1140 mg ÷ 5 mg/mL = 228 mL) at a rate of approximately 2.5 mL/min (228 mL ÷ 90 minutes) in 90 minutes.

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 the 10 mg/kg dose or the 3mg/kg dose, to complete the infusion in 90 minutes, with a 10-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 4 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 Cancer Treatment and Diagnosis, NCI, for this protocol.

8.1.11 Side Effects

See Section 5.3 (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 Alfa Interferon

8.2.1 Other Names

Interferon Alfa - 2b, Intron A, IFN-alpha 2b, NSC #377523

8.2.2 Classification

Biological response modifier.

8.2.3 Mode of Action

Interferon Alfa - 2b has antiviral, antiproliferative (cytostatic) and immunomodulatory properties. Its direct antiproliferative properties (e.g., inhibition of cell growth) may explain its activity in certain malignancies.

8.2.4 Storage and Stability

Interferon Alfa - 2b is provided as a lyophilized powder which must be reconstituted prior to administration. Unreconstituted drug vials bear expiration dates and are stored under refrigeration.

Reconstituted solutions of interferon Alfa - 2b are stable for 1 month at refrigeration temperatures and for 2 weeks at room temperature when reconstituted as directed by the manufacturer. Reconstituted solutions of interferon Alfa - 2b, left in the original vials, are stable for 1 month in the freezer and through 4 freeze-thaw cycles.

In plastic or glass syringes the drug is stable for 1 month frozen and through 2 freeze-thaw cycles. When interferon Alfa - 2b is reconstituted to a concentration ≥100,000 u/ml in normal saline, it is stable for only 24 hours at room or refrigeration temperatures.

NOTE: Intron A Solution for Injection is not recommended for intravenous administration and should not be used for the induction phase of malignant melanoma.

8.2.5 Dose Specifics

Induction Phase

For this study the induction phase is defined as the first 12 weeks of treatment, as follows:

Interferon Alfa - 2b, 20 MU/m²/d (rounded to the nearest 1.0 million unit) administered **IV** x 5 consecutive days out of 7 (e.g., M-F) every week x 4 weeks. Then, 10 MU/m²/d (rounded to the nearest 1.0 million unit) **subcutaneous** every other day (e.g., M,W,F) three times each week x 8 wks.

Maintenance Phase

Interferon Alfa - 2b, 10 MU/m²/d (rounded to the nearest 1.0 million unit) **subcutaneous** every other day (e.g., M,W,F) three times each week x 48 wks.

8.2.6 Preparation

The lyophilized product is reconstituted as directed by the manufacturer.

For intravenous injection, it is recommended that interferon Alfa - 2b be administered as a 100,000 U/mL solution to minimize adsorption of the drug to glass and plastic containers.

8.2.7 Administration

It is recommended that Interferon Alfa-2b be prescribed in 10 million unit vials (with instructions to reconstitute with 1 mL of diluent to reach a final concentration of 10:1).

However, other standard vial strengths are acceptable. Subcutaneous administration utilizes standard technique. The vial strength prescribed and final dose volume for each injection should be recorded in the comments section of the patient diary if self-administered. Intravenous dose should be diluted in sodium chloride 0.9% / 100 mL and given over 20 minutes.

8.2.8 Incompatibilities

Interferon Alfa - 2b is incompatible with 5% dextrose in water and with a component of the Travenol Infusor.

8.2.9 Compatibilities

Information regarding the compatibility, stability, etc. of drugs is constantly changing Consult your pharmacist to obtain the most up to date information. Interferon Alfa - 2b is compatible in normal saline, Ringer's injection, Lactated Ringers' and 5% sodium bicarbonate injection.

8.2.10 Availability

Interferon Alfa - 2b is a commercial product.

8.2.11 Side Effects

Flu-like symptoms: Fever, chills, diaphoresis and rigors occur universally regardless of dose, route or schedule. Usual onset is in 1-2 hours with peak in 4-8 hours and duration less than 18 hours. Symptoms tend to lessen with continued dosing.

Constitutional Symptoms: Fatigue, malaise, anorexia, weight loss, Raynaud's phenomenon, muscle pain, arthralgias, headaches; may be doselimiting, usually occurring during the first or second week of treatment.

Hematologic: Leukopenia, thrombocytopenia and anemia (uncommon).

Hepatic: Increased bilirubin, increased alkaline phosphatase, increased transaminases occasionally, hepatitis (uncommon).

Cardiovascular: Hypotension, hypertension, dizziness, syncope, arrhythmia (atrial or ventricular), tachycardia, congestive heart failure and myocardial infarction have been reported.

Neurologic: Somnolence, confusion with high doses; numbness, paresthesia, neuropathy; depression, personality disorder, psychomotor retardation, acute paranoid reactions, hallucinations, inability to concentrate, agitation, anxiety; visual disturbances, eye pain, hemianopsia, retinal infarction with vision loss (1 patient); sleep disturbances, insomnia; tremor, seizures, acute aphasia, coma, cerebral edema.

Gastrointestinal: Mild nausea, vomiting, diarrhea, dysphagia, anorexia, taste change, flatulence, constipation, abdominal pain and gastric distress have been reported.

Dermatologic: Alopecia, rash, pain at injection site, dry skin, flushing, urticaria, epidermal necrosis.

Renal: Proteinuria, microscopic hematuria, pyuria, azotemia, acute renal failure, nephrotic syndrome (1 patient), glycosuria, albuminuria, polyuria.

Pulmonary: Orthopnea, dyspnea, bronchospasm, cough, pulmonary edema/acute respiratory distress syndrome, pharyngitis.

Metabolic: Hyperglycemia, hypertriglyceridemia, hypothyroidism.

Coagulation: Increased PT, PTT.

8.2.12 Nursing Implications

Inform patient of expected side effects and reassure him/her that symptoms are not necessarily related to tumor progression.

Instruct patient in keeping a daily record of temperature, symptoms and activity level (Refer to E3611 Patient Diary - Interferon, Appendix III).

Review and document type, character and duration of side effects.

Fever, rigors and other flu-like symptoms: Acetaminophen administered prior to treatments and every four hours following the initial injections may decrease severity of symptoms. Nonsteroidal or steroidal anti-inflammatory agents should be avoided (as much as possible for this indication with IFN) since their effect on the immune system is not known.

Fatigue and CNS toxicity: Patient performance status and mental status should be assessed regularly and appropriate dose adjustments made per protocol. Instruct patient to arrange most important activities in the morning and allow for frequent rest periods.

Anorexia: Monitor weight regularly. Encourage patient to maintain adequate fluid, caloric and protein intake. Antiemetics as needed.

Granulocytopenia, thrombocytopenia, liver enzyme elevations: Monitor blood counts closely and modify dosage per protocol. Advise patient of special precautions regarding infection and/or bleeding when appropriate.

8.2.13 References

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9. Statistical Considerations

This is a phase II randomized study with a 2 by 2 factorial design with (i) no HDI vs. HDI (across Ipilimumab treatment status) and (ii) ipilimumab 3mg/kg vs. Ipilimumab 10mg/kg (across HDI treatment status). We hypothesize that HDI + ipilimumab treatment will lead to improved PFS in comparison to ipilimumab alone (primary hypothesis). An important secondary objective of this study is to assess toxicity data in the tested combinations of treatment. Other secondary objectives include to: (i) assess response rate and PFS for ipilimumab 10mg/kg treatment in comparison to ipilimumab 3mg/kg; (ii) assess OS in the tested combinations (no HDI vs. HDI) of treatment.

9.1 Endpoints and Sample Size

9.1.1 Primary Endpoint

Progression-free survival (HDI will improve PFS compared to no HDI).

To account for ineligible cases, 88 patients (for 80 eligible) will be accrued. Based on E1608 accrual, accrual is expected to be completed within 6 months and patients will be followed for additional 5 months.

The primary comparison will be PFS. Primarily, it is assumed that HDI will improve the median PFS from 3 to 6 months from no HDI. In addition, it is assumed 10mg/kg Ipi will improve the median PFS from 3 to 6 months from 3mg/kg Ipi. Based on the log-rank test, these comparisons will have at least 82% power at a two-sided type I error rate of 0.10.

The distribution of PFS will be compared using the log-rank test.

9.1.2 Secondary Endpoints

- Safety
- Overall survival (within the constraints of the sample size) for HDI versus no HDI
- Response rate by RECIST and by irRC. For this endpoint, irRC will be utilized as secondary and investigational criteria. The irRC data will be associated with the RECIST-based tumor response, PFS and OS.
- Assess RR, PFS and OS for ipilimumab 10mg/kg in comparison to ipilimumab 3mg/kg

Regimen limiting serious adverse events (RLE) would be defined as grade 3 or higher immune mediated adverse events that require steroids or immunosuppressive therapy and include the following: diarrhea/colitis, immune mediated hepatitis, endocrinopathies, skin toxicity (grade 4 or higher for skin), neuropathies, immune cytopenias or other grade 3 or higher immune mediated adverse events that require steroids or immunosuppressive therapy. We will evaluate the RLE rate for each treatment arm. In addition, OS data will be described for each treatment arm using the Kaplan-Meir method.

No formal interim analysis is planned as this study is expected to accrue rapidly (≤ 6 months) and has a short additional follow-up time (< 6 months). However, toxicity data will be monitored and reviewed carefully on a monthly basis.

Toxicity Monitoring:

The population for the safety analysis will be comprised of all patients who received at least one dose of study medication. Patients will be monitored for adverse events using the National Cancer Institute's (NCI) Active Version of the Common Terminology Criteria for Adverse Events (CTCAE) version 4. All treatment-emergent and baseline adverse events and hematological/biochemical toxicities based on laboratory measurements, as well as drug related AE's, will be summarized by treatment group and NCI CTCAE worst grade.

In regards to toxicity management during the study, TOXICITY MANAGEMENT GUIDELINES for both HDI and Ipilimumab have been adopted and described in detail in the study protocol.

Specific guidelines for managing ipilimumab-related toxicities on an end-organ basis have been provided as part of this study. An ipilimumab toxicity management training module will be made available to study investigators.

A monthly conference call between ECOG-ACRIN investigators will be conducted to review the adverse events reported. Toxicity data will be monitored and reviewed carefully on a monthly basis. Incidence data of specific toxicity type as well overall worst degree toxicity data will be summarized and compared between the two arms. The result of this analysis will be discussed with the ECOG-ACRIN Data Monitoring Committee.

9.2 Stratification

Stage: III/M1a, M1b, M1c

9.3 Gender and Ethnicity

Based on previous data from E1608/E1602/E2603/E3695 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	32	56	88
Ethnic Category: Total of all subjects	32	56	88
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
White	31	56	87
Racial Category: Total of all subjects	32	56	88

Overall Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DMC 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 DMC 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 DMC. Any DMC 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 DMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

Rev. 5/15

10. Pathology Review

Pathology samples must be submitted for review and classification (baseline only) and for future laboratory studies. Submission of pathology samples for diagnostic review is mandatory in order for the patient to be considered evaluable. If insufficient material is available after diagnostic pathology, the pathologist must contact the Study Chair and send a letter and pathology report stating this to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Diagnostic materials will be forwarded to Dr. Uma Rao for central review.

The submitting pathologist and clinical research associate should refer to Appendix I (Pathology Submission Guidelines) for guidelines and summary of submission requirements.

10.1 Pathology Materials Required For This Protocol

ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.3.

1. Forms to be submitted with all tissue submissions:
   - ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the type of material submitted and (i.e., paraffin block, slide sub number A, B, etc.) clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
   - A copy of the surgical pathology report
   - Immunologic studies, if available
   - Sample Tracking System Shipping Manifest Form (see Section 10.3)

   In addition to the surgical pathology report, if immunologic studies have been performed at the home institution, it is necessary that these be forwarded as well.
2. Mandatory Pathology Submission for Diagnostic Review
   - Primary Melanoma (for patients with known primary cutaneous melanoma)

   One (1) H & E of the primary melanoma and fifteen (15) unstained slides preferably from the thickest portion of the tumor for immunostains (please do not deparaffinise slides) OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request. If the patient has more than one primary lesion, please include above slides and/or block for each primary.

   NOTE: Sections of surgical margins of skin, unless positive for tumor, are not required. A surgical pathology report is sufficient.

   - Regional Lymphadenectomy Specimen

   One (1) H & E section of the tumor bearing lymph nodes ONLY, with a copy of pathology report. An alternative is to send two (2) unstained slides or two (2) H & E slides on each positive lymph node. Pathology report should indicate:

a. Total number of lymph nodes
b. Number of lymph nodes positive
c. Size of the largest lymph node
d. Whether there was gross soft tissue tumor involvement
e. Whether there was evidence of extra-capsular spread
f. Whether a lymph node was a sentinel lymph node

(Please include report on immunostains if any).

- In-transit or satellite metastases, or distant cutaneous metastases, or distant lymph node metastases, or lung or other visceral metastases

  One (1) H & E section of the metastatic lesion and fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

3. Progression/Relapse Biopsy (if performed, for future laboratory studies per patient consent)

   - One (1) H & E section of the metastatic lesion and fifteen to twenty (15-20) unstained slides from the thickest part of the tumor, or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

     NOTE: A copy of the completed submission form will be sent to the ECOG-ACRIN Operations Office - Boston by the Central Biorepository and Pathology Facility.

Rev. 5/15

10.2 Shipping Procedures

The required diagnostic materials must be submitted within one month of patient randomization.

The optional pathology samples from progression/relapse should be submitted within one month of disease progression.

Access to the shipping account for specimen 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 provided 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.

Shipping Address

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

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

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all samples 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 samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Rev. 5/14

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 generated and shipped with all sample submissions.

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

Study Specific Notes

An Generic Specimen Submission Form (#2891) will be required only if STS is unavailable at the time of sample submission. Indicate the appropriate Lab ID # on the submission form:

- ECOG-ACRIN Central Biorepository and Pathology Facility
- 0009= ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory

The day of shipment, notify the IMCPL 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 FedEx tracking number.

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

11. Submission of Samples

Blood samples are being collected for future use in laboratory corollary studies, including the performance of novel biomarker evaluations that are of prognostic and therapeutic predictive value. Due to the potential future therapeutic predictive implications (targeting treatment to those who are likely to benefit) and economic implications (avoiding the toxicities and cost for those who are not likely to benefit) of such studies, patients are encouraged to participate. However, participation in providing these blood samples is optional.

ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.3.

Rev. 5/15

11.1 Sample Submission Schedule

Blood should be collected as specified below for each tube type at:

- baseline (prior to treatment)
- day 19 (+ 4 day window)
- after twelve (12) weeks of initiating treatment (+/- 1 week)
- 48 weeks
- disease relapse (if relapse occurs earlier than 48 weeks).

No further blood samples are to be submitted after the relapse blood is sent.

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

Instructions to order kits are outlined in Section 11.3

Questions are to be directed to the Immunological Monitoring and Cellular Products laboratory (IMCPL) ECOG-ACRIN study coordinator at (412) 624-0078.

11.2 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 E3611
- ECOG-ACRIN five-digit patient sequence number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

1. At EACH time point please submit the following:
    - Three (3) 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).

2. Baseline, Day 19 [+4 day window] and after and twelve (12) weeks of initiating treatment ONLY, please submit the following:
   - One (1) FULL PAXgene RNA tube (Fisher #23 021 01).
3. At Baseline ONLY please submit the following:
   - One (1) FULL 10 cc YELLOW top ACD tube (BD cat # 364606)

11.3 Shipping Kits

Specimen shipping kits must be requested from the IMCPL. Please fax the request using the Shipping Kit Request Facsimile Form (Appendix VI) to (412) 623-6625 or call the IMCPL at (412) 624-0078. Please allow ten 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 shipping instructions provided in the kit carefully.

The shipping kit consists of the following:

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

11.4 Shipping Procedures

Log the samples into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, a Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

If the STS is unavailable, notify the IMCPL 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.

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). The red, yellow, and PAXgene RNA tubes should be refrigerated immediately and shipped at 2-8°C. 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

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

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

11.5 Use of Specimens in Research

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the mandatory diagnostic reviews, will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility and the ECOG-ACRIN Immunologic Monitoring and Cellular Products Laboratory.

Rev. 5/15

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but are not limited to, extradition of plasma, serum, DNA and RNA.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future 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.

11.6 Sample Inventory Submission Guidelines

Inventories of all specimens collected and aliquoted will be submitted electronically by secure web application to the ECOG-ACRIN Operations Office - Boston on a monthly basis or upon request by any laboratory holding and/or using specimens associated with this study.

12. Electronic Data Capture

Please refer to the E3611 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.

12.1 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.

13. Patient Consent and Peer Judgment

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

14. References

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A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E3611
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 5/15

Rev. 5/15

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material, to the appropriate pathologist.
2. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG-ACRIN Generic Specimen Submission Form (#2981). If any other reports are required, they should be obtained from the appropriate department at this time.
3. Keep a copy of the ECOG-ACRIN Generic Specimen Submission Form (#2981)for your records. (The original should be sent to the CBPF.)
4. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)
   Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.
5. 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 1-844-744-2420or by emailing eacbpf@mdanderson.org.

Rev. 5/15

List of Required Material

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination With High Dose Interferonα in Advanced Melanoma

Baseline (submit within one month of patient randomization)

1. ECOG-ACRIN Generic Specimen Submission Form (#2981).
2. Institutional pathology report (must be included with EVERY pathology submission)
3. Pathology Materials:
   - Primary Melanoma (for patients with known primary cutaneous melanoma):
     - One (1) H & E of the primary melanoma and fifteen (15) unstained slides preferably from the thickest portion of the tumor for immunostains (please do not deparaffinise slides) OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request. If the patient has more than one primary lesion, please include above slides and/or block for each primary.
   - Regional Lymphadenectomy Specimen:
     - One (1) H & E section of the tumor bearing lymph nodes ONLY, with a copy of pathology report. An alternative is to send two (2) unstained slides or two (2) H & E slides on each positive lymph node. Pathology report should indicate:
       a. Total number of lymph nodes
       b. Number of lymph nodes positive
       c. Size of the largest lymph node
       d. Whether there was gross soft tissue tumor involvement
       e. Whether there was evidence of extra-capsular spread
       f. Whether a lymph node was a sentinel lymph node

       (Please include report on immunostains, if any).

       In addition, please include fifteen to twenty (15-20) unstained slides from the thickest part of the tumor OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.
   - In-transit or satellite metastases, or distant cutaneous metastases, or distant lymph node metastases or lung or other visceral metastases:
     - One (1) H & E section of the metastatic lesion and fifteen to twenty (15-20) unstained slides from the thickest part of the tumor OR, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

   NOTE: Sections of surgical margins of skin, unless positive for tumor, are not required. A surgical pathology report is sufficient.

   NOTE: A copy of the completed submission form will be sent to the ECOG-ACRIN Operations Office - Boston by the Central Biorepository and Pathology Facility.

NOTE: Submission of pathology samples for diagnostic review is mandatory in order for the patient to be considered evaluable.

Progression/Relapse (submit within one month of disease progression)

1. ECOG-ACRIN Generic Specimen Submission Form (#2981).
2. Institutional pathology report (must be included with EVERY pathology submission)

   If biopsy was performed submit:

   - One (1) H & E section of the metastatic lesion and fifteen to twenty (15-20) unstained slides from the thickest part of the tumor or, if the primary pathologist is willing, please request the corresponding block, which will be promptly returned upon request.

MEMORANDUM

TO:
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE:

SUBJECT: Submission of Pathology Materials for E3611: *A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination With High Dose Interferon-α in Advanced Melanoma*

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 laboratory studies.**

Please complete PART B of the Submission Form. Keep a copy of the submission form for your records and return the surgical pathology report(s), the slides and/or blocks and any other 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/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future laboratory studies. Blocks will be returned for future purposes of patient management upon request.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420or EMAIL eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

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

9/12/14

A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced 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],

Rev. 5/14

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 Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix III

Patient Interferon Diary

Diary Card

Interferon

Dates: ____/____/____ to ____/____/____

Patient Number: _____

Patient Initials:_____

ECOG-ACRIN patient sequence number:

Dose No.	Date			TIME Record Time of Dose (Circle AM or PM)					Use the space below to make notes about things you would like to tell the doctor (include any unusual symptoms you experience, other medicine you have taken and anything else you think may be of interest.
	Month	Day	Year						
1						:		AM PM	
2						:		AM PM	
3						:		AM PM	
4						:		AM PM	
5						:		AM PM	
6						:		AM PM	
7						:		AM PM	
8						:		AM PM	
9						:		AM PM	
10						:		AM PM	
11						:		AM PM	
12						:		AM PM	
13						:		AM PM	
14						:		AM PM	
15						:		AM PM	
16						:		AM PM	
17						:		AM PM	
18						:		AM PM	
19						:		AM PM	
20						:		AM PM	
21						:		AM PM	
22						:		AM PM	
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25						:		AM PM	
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27						:		AM PM	
28						:		AM PM	
29						:		AM PM	
30						:		AM PM	

A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix IV

E3611 Cooperative Research and Development Agreement (CRADA)

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order, as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix V

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.

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix VI

Shipping Kit Request Facsimile Form

ECOG-ACRIN – PROTOCOL E3611

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:

Baseline (10GT/3RT/1ACD/1PAX) _____

Day 19, Week 12 (10GT/3RT/1PAX)_____

Week 48 or Relapse (10GT/3RT) _____

Shipping Address: _____

_____

_____

_____

PLEASE ALLOW 10 WORKING DAYS FOR RECEIPT OF SHIPPING KITS

NOTE: To order collection and shipping kits for E3611, patients must be registered to or in the process of being worked up for the E3611 trial. Due to funding restrictions institutions cannot order multiple collection and shipping kits in advance.

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix VII

Specimen Shipment Requisition Form

ECOG-ACRIN – PROTOCOL E3611

It is required that samples submitted from patients participating in E3611 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 specimens by overnight express 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 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)

Time Points (check one):

☐	Baseline	Three (3) red top tubes, Ten (10) green top tubes, One (1) PAXgene RNA tube and One (1) ACD yellow top tube
☐	Day 19	Three (3) red top tubes, Ten (10) green top tubes, One (1) PAXgene RNA tube
☐	12 weeks	Three (3) red top tubes and Ten (10) green top tubes, One (1) PAXgene RNA tube
☐	48 weeks	Three (3) red top tubes and Ten (10) green top tubes
☐	Relapse	(3) red top tubes and Ten (10) green top tubes

Shipping checklist: (kits will be shipped / delivered to you from UPCI IMCPL upon request)

____ Label vials with patient initials/sequence number, and date and time of draw.

____ Seal, wrap, and place specimen tubes in specimen shipper kit.

____ STS Shipping Manifest Form. Make a copy for your records and place the original form inside the specimen shipper kit.

To be completed by IML Staff:	IML Study Number
IML Accession Number:	Specimen Type received (if different from above):
Specimen Acceptability:	Comment:

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix VIII

Administration of Interferon (Directions for Administration of Subcutaneous Doses)

Patients deemed competent to self administer the Interferon may do so. The hospital or clinic staff will instruct the patient or interested family member in this technique. Patients should be allowed to administer these injections at home when they can independently perform a return demonstration for their instructor. The instructor will note this fact in the patient's record. Adequate contact persons and telephone numbers should be provided so that the patient will always be able to reach someone familiar with this procedure should they need assistance.

For emergency contact: _____

(insert site contact information)

Instructions for Self-Administering Medication

1. Preparation

a. Wash hands well. Take required dose of acetaminophen (Tylenol®).

b. Assemble necessary supplies. The Interferon should be kept refrigerated until several minutes before each treatment. You also need a syringe with a needle, at least 3 alcohol prep pads, and a container (an unbreakable, leak-proof, reclosable container - milk carton, coffee can) for used materials.

2. Reconstituting the Interferon Powder

a. If this is the first dose that will be coming from a vial, the Interferon powder must be dissolved, using the diluent provided. Snap the plastic cap off both vials, and cleanse both rubber stoppers with an alcohol pad and allow to air dry.

b. There may be a different syringe/needle provided that you will use to reconstitute the Interferon. Open the package containing one of these syringes and attach (or tighten) the appropriate needle to it. Pull back the plunger of the syringe so that the top of it rests right on the line representing the volume of diluent that you are to add to the Interferon powder.

c. Insert the needle through the stopper of the diluent vial, and invert the vial/syringe in front of you at eye level, holding the syringe in your dominant hand and the vial in the other.

d. Inject the air from the syringe into the vial slowly. If you feel like you are forcing it, pull back the plunger to allow some solution into the syringe, then push the remaining air into the vial. Ultimately, your syringe should be filled with diluent solution up to the correct line and no air will be left in the syringe. If you have bubbles, tap the syringe with your finger until they rise to the top, push them up into the vial and recheck the plunger to insure that it is still at the correct volume mark.

e. Withdraw the needle from the diluent vial and insert it into the vial containing the Interferon powder. This time keep the vial on the surface and push the plunger down to inject the diluent into the powder vial. If you meet resistance, allow some air to rise into the syringe before pushing down and expelling the remaining solution into the vial. Eventually, all the solution will be in the vial. Pull back the plunger to return it to the line that is the same as the volume of solution that you injected. This will prevent pressure build-up in the Interferon vial. Remove the needle and discard it appropriately.

f. To help dissolve the Interferon powder, you may need to roll the vial between your palms or swirl the solution around. DO NOT shake the vial. Be sure that all the powder is dissolved before proceeding to #3.

3. Withdrawing Your Dose From the Vial

a. Cleanse the rubber stopper of the vial containing the Interferon solution with an alcohol pad and allow to air dry.

b. Open syringe package and needle package (if separate) and attach or tighten needle by twisting until tight. Pull back the plunger to the mark that represents your dose (i.e., 3 mU/0.5 ml, top of plunger should rest at the 0.5 ml mark). This fills the syringe with air in a volume equal to the volume of your dose.

c. Uncap the needle and push it through the stopper, at least half-way into the vial. Now pick up the vial (with syringe/needle in it) with your left hand and turn it upside down, holding it at eye-level, about 12 inches from your face. You should now have the vial in one hand and your other hand free to manipulate the syringe. (Note: Left-handed persons should have the vial in their right hand, so that they can manipulate the syringe with their left hand.)

d. Inject air from the syringe into the vial slowly, and then withdraw the plunger. The syringe will gradually fill with drug solution. Repeat this procedure until only solution is in the syringe, solidly, to the mark that indicates your dose. Withdraw needle and recap it.

4. Administration

a. Thoroughly clean the area to be injected with an alcohol pad. Areas appropriate for this type of injection have been shown to you. A new site should be used for each injection whenever possible.

b. As demonstrated, pinch 1½ to 2 inches of loose skin from the site to be injected.

c. Uncap the needle, and insert the needle approximately ¼ inch into the skin and push the syringe plunger in all the way, thereby giving the dose of Interferon.

d. Remove needle and wipe injection site with a new alcohol pad, but do not massage the area to any great extent.

e. Needles are not to be recapped. Used needles and used syringes should be disposed of in the proper disposal container provided by your pharmacy and returned to the clinic pharmacy for disposal. If the Interferon vial contains more than one dose, write the date on the label. It is usable for 30 days. INTRON A injection vials should be stored in the refrigerator between 2° and 8° C (36° and 46°F), not in the freezer.

f. If a drug administration diary has been provided, remember to complete it after each dose. Enter the date and time of day given, along with any notable side effects that you may have experienced since previous dose was given. Also record vial strength and dose volume at each entry.

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-α in Advanced Melanoma

Appendix IX

TNM Staging for Melanoma

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a. without ulceration b. with ulceration
T3	2.01-4.00	a: without ulceration b: with ulceration
T4	> 4.00	a. without ulceration b: with ulceration
N		
	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometatasis* b: Macrometastasis†
N2	2-3	a: Micrometatasis* b: Macrometastasis† c: In transit metastases/ satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/ Satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase,
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2. Anatomic Stage Groupings for Cutaneous Melanoma

	Clinical Staging*				Pathological Staging†		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N> N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Reference: Balch CM,et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36):6199-206.

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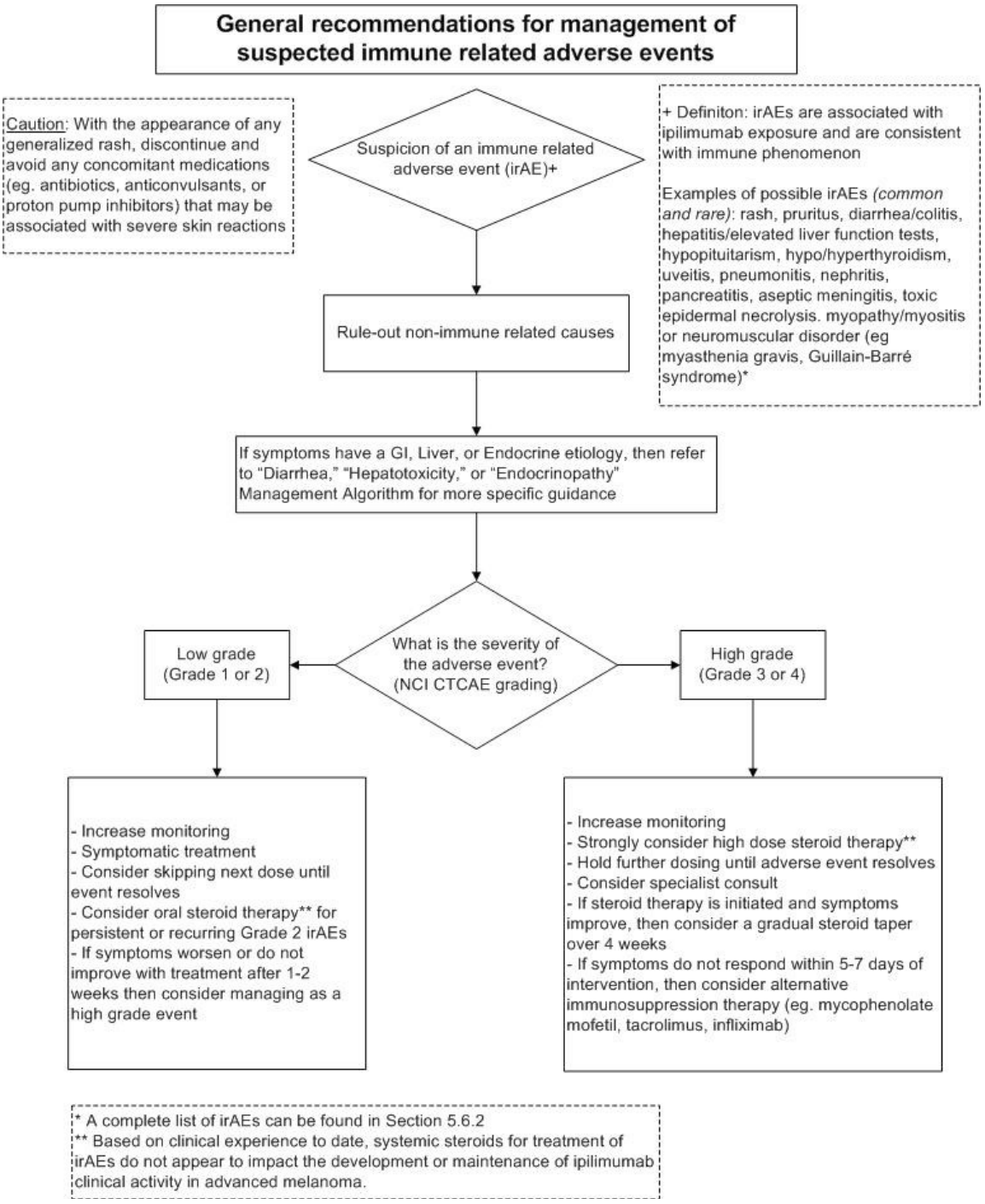
Appendix X

General Recommendations for immune-related Adverse Events (IrAEs)



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Appendix XI

Suggested Work-up and Treatment for Immune-Related Adverse Events (irAEs)

An IRAE is defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event a non-dermatologic, immune-mediated event. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Documentation of test results should be included in the patient's medical record.

Gastrointestinal (diarrhea) and skin (rash)-related toxicities have been the most common IRAEs noted in prior studies with ipilimumab. Suggested work-up procedures for suspected IRAEs of the gastrointestinal tract, liver, skin, eye, pituitary, and adrenal gland are listed below. When symptomatic therapy is inadequate or inappropriate, an IRAE should be treated with steroids followed by a slow taper.

Gastrointestinal Tract: Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. An algorithm for working up patients with diarrhea or suspected colitis is provided in Appendix XII.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count; or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with 3 to 5 specimens for standard paraffin block be performed. If possible, 1 to 2 biopsy specimens should be snap frozen and stored. All patients with confirmed colitis should also have an opthomological examination, including a slit-lamp exam, to rule out uveitis. Tests should also be performed for WBCs and for stool calprotectin.

Patients with colitis should discontinue any non-steroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms. Investigators should use their clinical judgment as to whether corticosteroids are necessary to treat colitis associated with ipilimumab therapy and as to what dose should be used. As guidance prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms and the dose should be gradually tapered over at least one month in duration. Lower doses of prednisone may be considered for less severe cases of colitis. It is suggested that prednisone (for oral administration) or solumedrol (for intravenous administration) be corticosteroid of choice in the treatment of colitis.

Liver: Elevation of LFTs ≥ 3 fold from baseline should instigate an investigation into the underlying etiology for suspected IRAEs. Neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile duct should be performed to rule out neoplastic or other causes for the increased LFTs. An ANA, pANCA, and anti-smooth

muscle antibody test should be performed if an autoimmune etiology is considered. Consultation with a hepatologist is appropriate for a suspected liver IRAE and a biopsy should be considered.

Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug.

Pancreas: Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may rarely be associated with anti-CTLA-4 monoclonal antibody administration. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include serum amylase and lipase tests.

Skin: A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Any non protocol drugs that could contribute to a drug reaction should be stopped if possible pending evaluation. Patients with low-grade ipilimumab-mediated skin toxicity (Grade 1 or 2) may remain on therapy and could be treated with symptomatic therapy (e.g., antihistamines). Low-grade symptoms persisting for 1 to 2 weeks and relapsing should be treated with topical or moderate dose oral corticosteroid therapy (e.g., prednisone 1 mg/kg once daily or equivalent). High-grade (Grade 3 or 4) symptoms require high-dose IV corticosteroid therapy (e.g., methylprednisolone 2 mg/kg once or twice per day or equivalent) to control initial symptoms. A skin biopsy should be performed if appropriate. Once rash or pruritis is controlled, the initiation of corticosteroid taper should be based on clinical judgment; however, the corticosteroid dose should be gradually tapered over a period of at least 1 month.

Patients with any high-grade skin related toxicity (Grade 3 regardless of causality) have to skip ipilimumab and may only continue treatment with ipilimumab if the initial symptoms have improved to ≤ Grade 1, while patients with grade 4 skin toxicities have to permanently discontinue ipilimumab.

Eye: An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers and retina; visual field testing and an electroretinogram should also be performed. Patients with ipilimumab related uveitis or episcleritis have been treated with topical corticosteroid eye drops.

Endocrine: Subjects with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, intravenous corticosteroids with mineralocorticoid activity (e.g., methylprednisolone) should be initiated immediately. If the patient's symptoms are suggestive of an endocrinopathy but the patient is not in adrenal crisis, endocrine laboratory results should be evaluated before corticosteroid therapy is initiated.

Endocrine work up should include at least Thyroid stimulating hormone and free T4 levels to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Radiographic imaging (e.g., MRI) with pituitary cuts should be performed. If the pituitary scan and/or endocrine laboratory tests are abnormal suggestive of pituitary endocrinopathy, a short course of high dose corticosteroids (e.g., dexamethasone 4 mg every 6 hours or equivalent) should be strongly considered in an attempt to treat the presumed pituitary inflammation, but it is currently unknown if this will reverse the pituitary dysfunction. Abrupt discontinuation of corticosteroids should be avoided due to possible prolonged adrenal suppression. Once symptoms or laboratory abnormalities are controlled, and overall patient improvement is evident, the initiation of steroid taper should be based on clinical judgment; however the corticosteroid dose should be gradually tapered over a period of at least 1 month. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented, and it is possible that subjects may require life-long hormone replacement.

Patients diagnosed with hypophysitis should be permanently discontinued from additional ipilimumab therapy.

Suspected irAEs should be documented in the patient's medical record.

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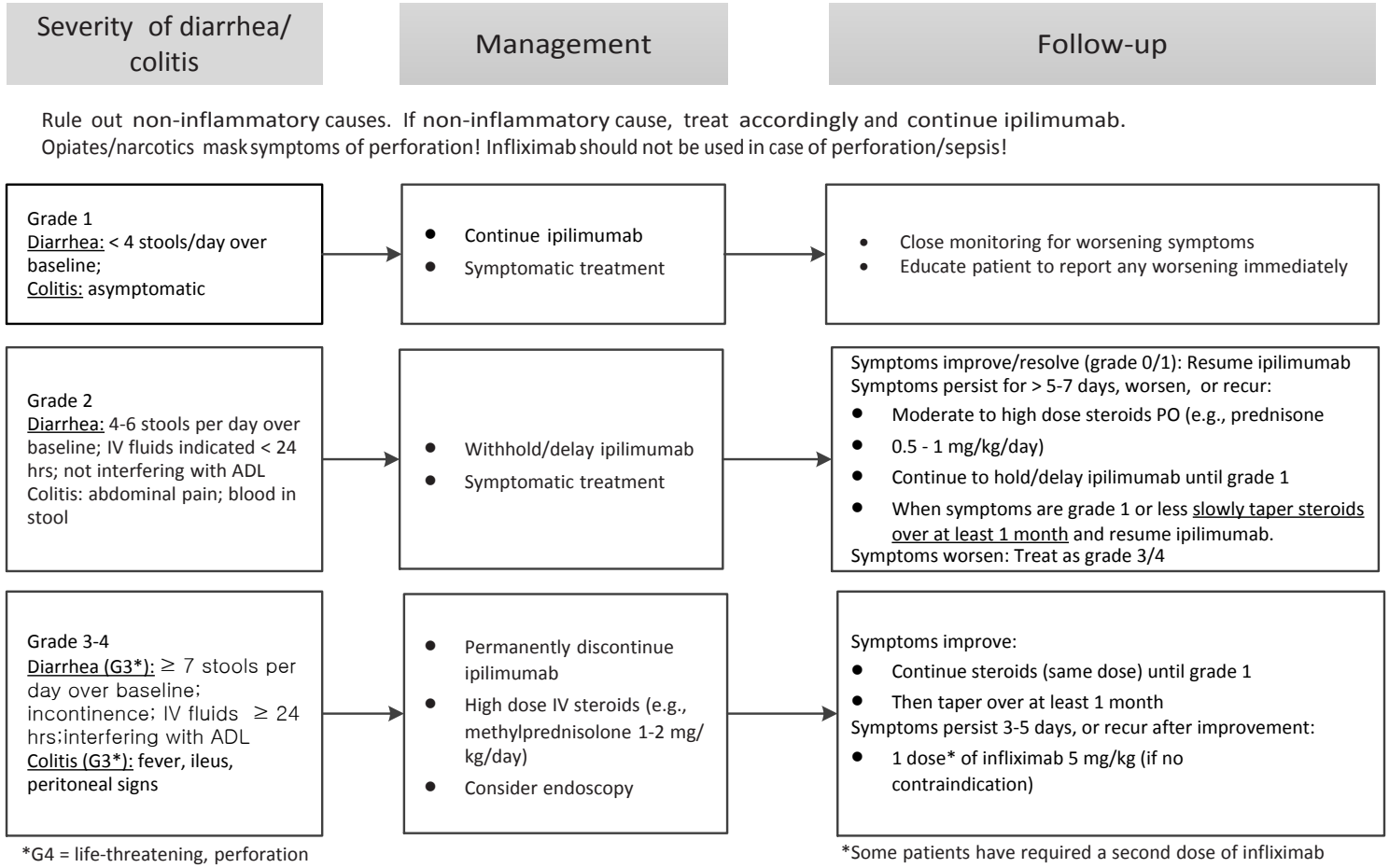
Appendix XII

Diarrhea 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.

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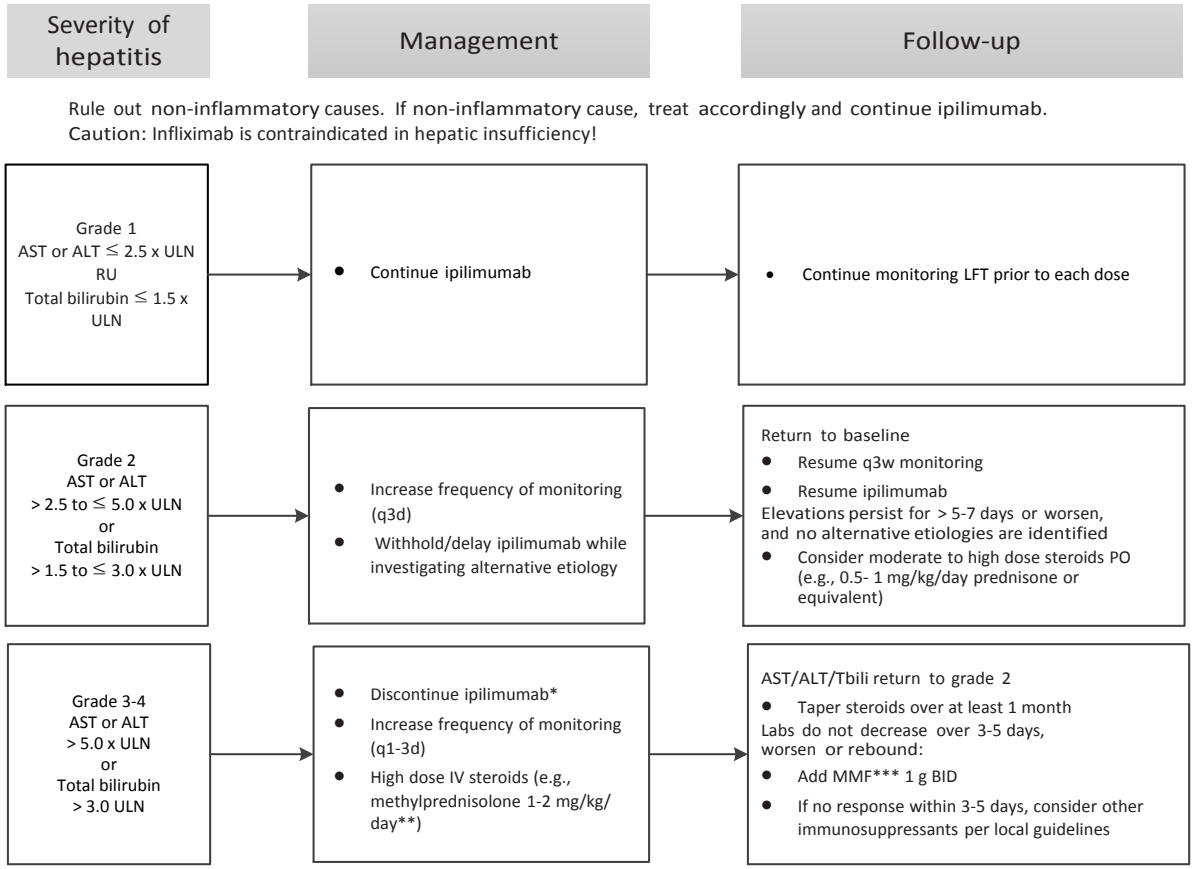
Appendix XIII
Hepatotoxicity Management Algorithm

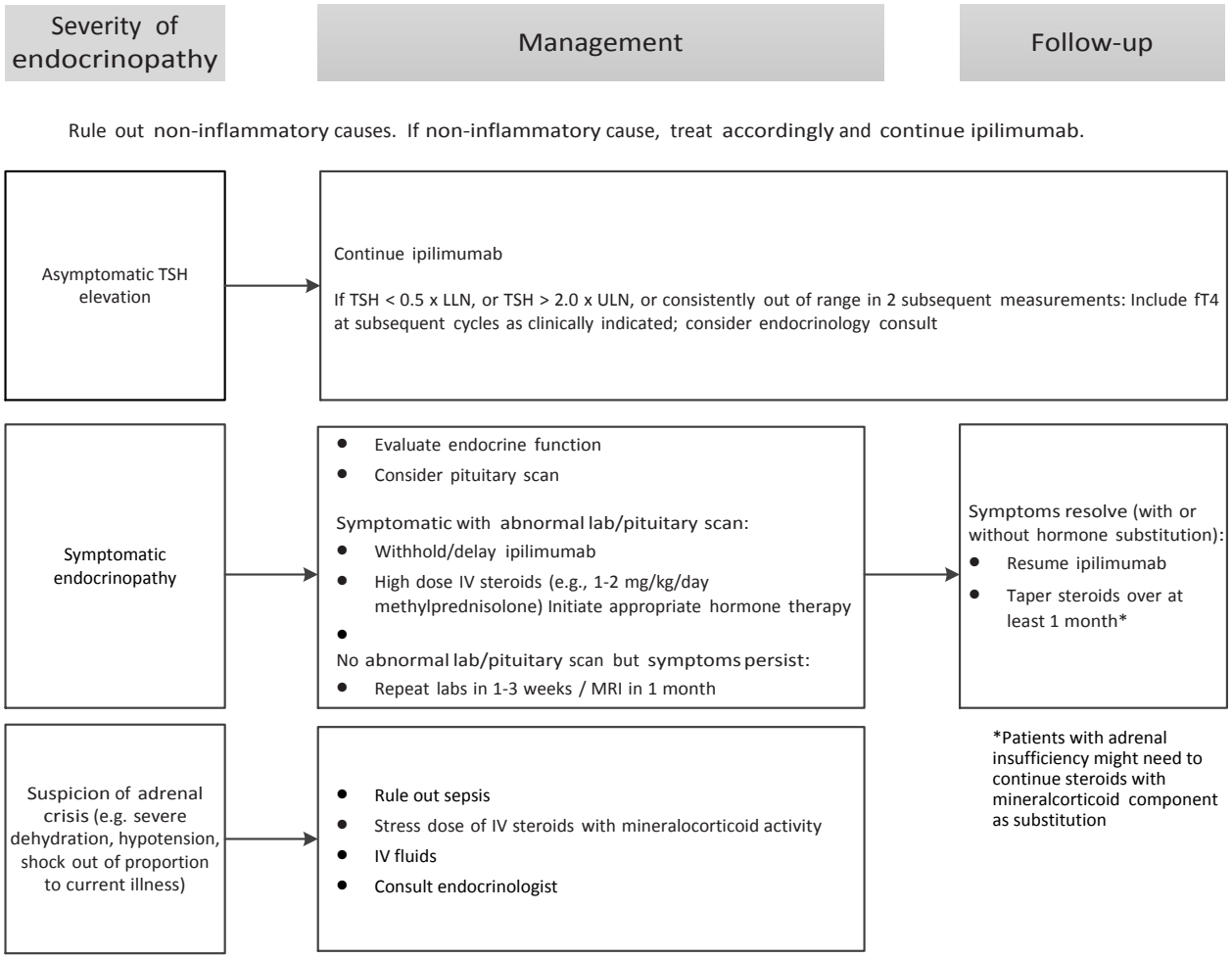


*Ipilimumab may be held/delayed rather than discontinued if AST/ALT ≤ 8 x ULN and Tbili ≤ 5 x ULN. Resume ipilimumab when AST/ALT/ Tbili return to grade 2 and meet protocol specific retreatment criteria.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.
*** MMF, 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.

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination With High Dose Interferon-α in Advanced Melanoma

Appendix XIV
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.

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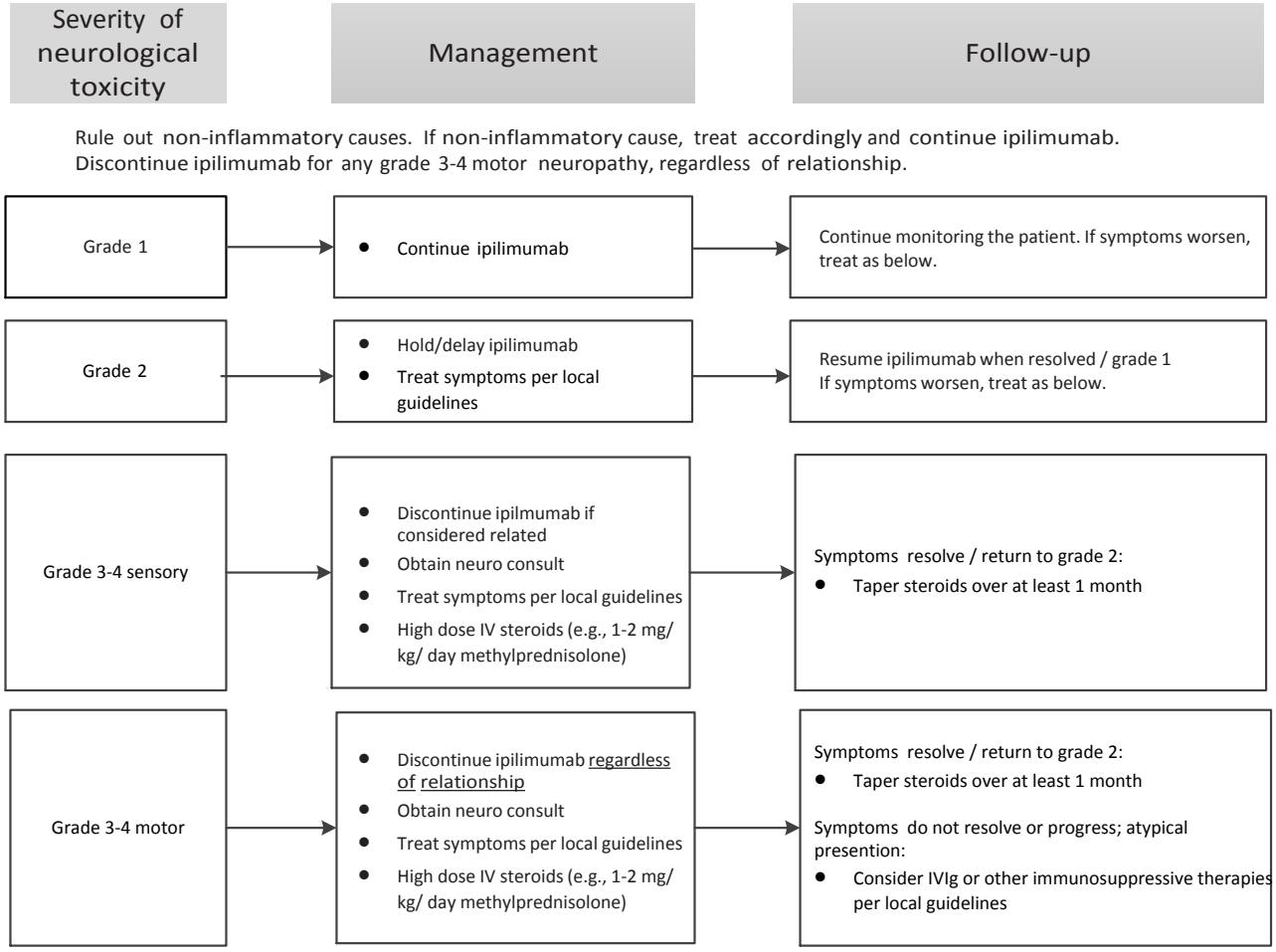
Appendix XV
Neuropathy Management Algorithm



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.

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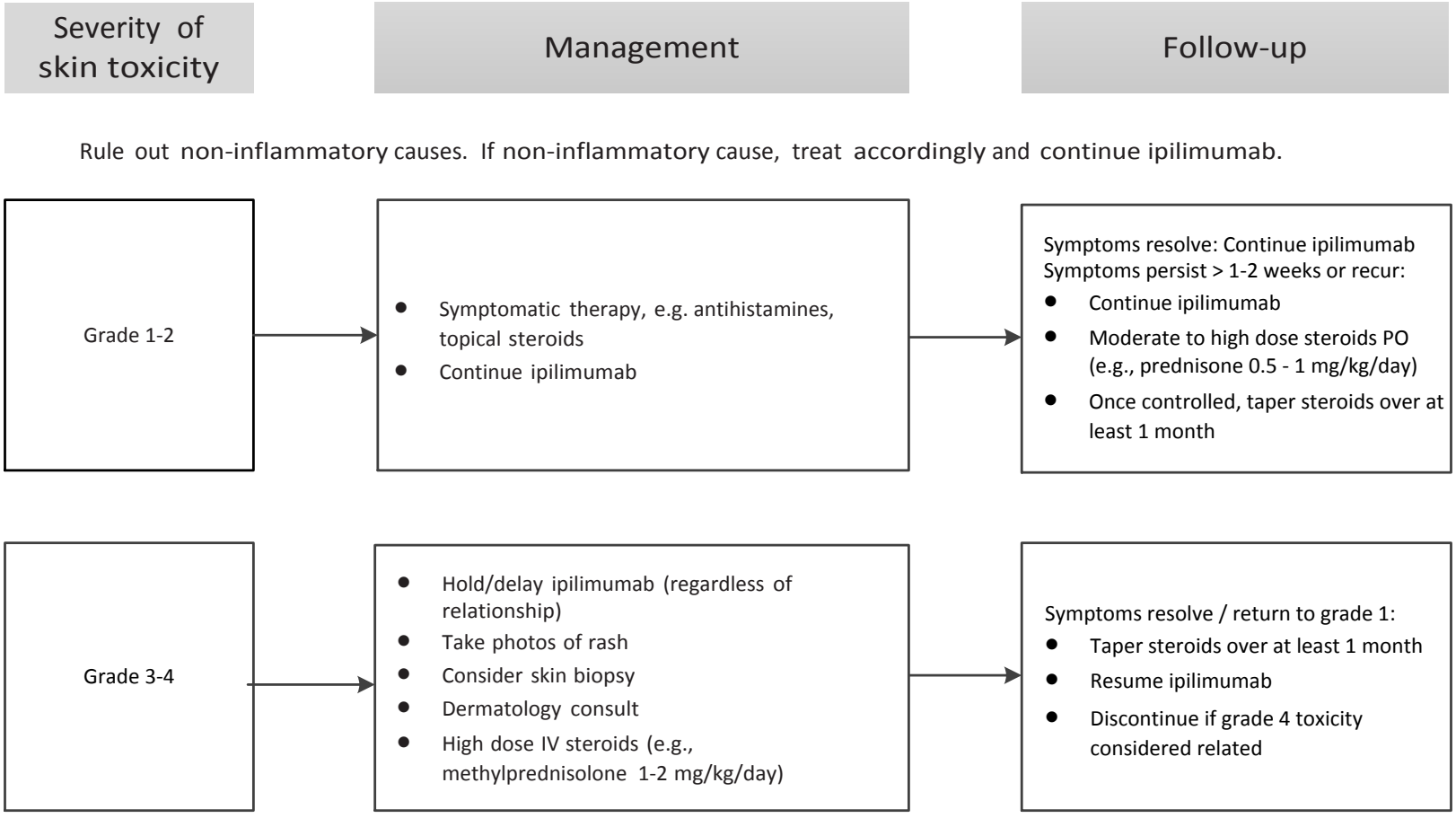
Appendix XVI
Skin Toxicity Management Algorithm



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 corticosteroids.

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Appendix XVII

Rev. 5/14

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

Rev. 5/15 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 Interferon-Alfa, or within 28 days of the patient's last dose of Ipilimumab or Interferon-Alfa 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 Fetal Death

A fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (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.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" 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
Rev. 5/15 or Interferon-Alfa must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "General disorders and administration - Other (neonatal loss)"under the System Organ Class (SOC) "General disorder and administration".

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)