Ohio State University

A phase 2 study using stereotactic ablative radiation therapy and ipilimumab in patients with oligometastatic melanoma

Primary Investigator: ***Jose Bazan M.D.***
Department of Radiation Oncology
James Cancer Hospital & Solove Research Institute
460 W. 10th Avenue
2nd Floor
Columbus, OH 43210
Phone: (614) 293-8415
Fax: (614) 366-8707
Email: Jose.Bazan2@osumc.edu

Bristol-Myers Squibb, Co.

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List of Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AE	adverse events
ALC	Absolute lymphocyte count
ACTH	Adrenocorticotropic hormone level
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the curve
BMS	Bristol-Myers Squibb
BORR	best overall/objective response rate
BW	body weight
CBC	complete blood count
CDCC	complement-dependent cellular cytotoxicity
CI	confidence interval
CHO	Chinese hamster ovary cell
CL	systemic clearance
CTLA-4	cytoxic T lymphocyte antigen 4
cm	centimeter
Cmax	maximum concentration
Cmin	minimum concentration
CMP	comprehensive metabolic panel
COMPTV	center of mass of the planned target volume
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTV	clinical target volume
DCR	disease control rate
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSMC	Data and Safety Monitoring Committee
DTIC	dacarbazine
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
ESR	expedited safety report
EU	European Union

FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
g/dL	grams per deciliter
GI	gastrointestinal
g/L	grams per liter
GTV	gross tumor volume
Gy	Gray
HCG	human chorionic gonadotropin
HepB	hepatitis B
HepC	hepatitis C
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLA-DR	human leukocyte antigen-disease resistance
hr	hours
HR	high risk
HRT	hormone replacement therapy
IB	investigational brochure
ICH	International Conference on Harmonisation
IDO	indoleamine 2,3-dioxygenase
IEC	International Education Council
IgG1	human immunoglobulin G
IMRT	intensity modulated radiation therapy
IND	investigational new drug
Ipi	ipilimumab
ir	immune-related
irAE	immune-related adverse effects
irBOR	immune-related best overall response
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related response criteria
irSD	immune-related stable disease
irSPD	immune-related sum of product diameter
IRB	investigational review board
ITT	insulin tolerance test
ITV	intensive therapy unit
IU/L	International Unites per liter
IV	intravenous

kg	kilogram
L	liter
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
mcg/mL	micrograms per milliliter
mg	milligram
mg/dL	milligrams per deciliter
mg/kg	milligrams to kilograms
mg/kg/day	milligrams per kilogram per day
mg/m^2	milligrams per metered square
mIU/mL	milli international units per milliliter
mL	milliliter
MLC	multi-leaf collimator
mL/h	milliliters per hour
mL/h/kg	milliliters per hours per kilogram
mL/min	milliliter per minute
mm	millimeter
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MR	magnetic resonance
mRNAs	micro ribonucleic acids
MV	megavoltage
Mwho	modified World Health Organization
NCA	non-compartmental analysis
NCI	National Cancer Institute
NYHA	New York Heart Association
OAR	organs at risk
OR	overall response
OS	overall survival
OSUCCC	Ohio State University Comprehensive Cancer Center
PAP	
PET/CT	positron emission tomography-computed tomography
PFS	progression-free survival
PHA	
PHI	protected health information
PI	primary investigator
PK	pharmacokinetic
PPK	population pharmacokinetics
PR	partial response

PS	performance status
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PTV	planned target volume
q3w	every three weeks
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase II dose
RTOG	Radiation Therapy Oncology Group
SABR	stereotactic ablative radiation therapy
SAE	serious adverse event
SD	stable disease
SPD	sum of the products of diameters
SRS	slow-reacting substance
SUSAR	suspected, unexpected serious adverse reaction
SWOG	Southwest Oncology Group
TA	tumor assessment
TAA	tumor-associated antigen
TMA	tissue microarray
ug/mL	microgram per milliliter
uL	microliter
ULN	upper limit of normal
USP	acetic acid solution
Vss	volume of distribution at steady-state
WBC	white blood cell
WOCBP	women of childbearing potential

Study Summary

Title	A phase II study using stereotactic ablative radiation therapy (SABR) and ipilimumab in patients with oligometastatic melanoma
Short Title	SABR and ipilimumab in oligometastatic melanoma
Protocol Number	***OSU #12182*** ***IRB # 2013C0096***
Phase	2
Methodology/Study Design	Phase II, single-arm, open label, non-randomized study with stereotactic ablative radiation therapy and ipilimumab as outlined in the treatment plan. We will perform a phase II trial with a primary endpoint of progression-free survival.
Study Duration	24 months
Study Center(s)	Single center
Objectives	*Primary Objectives:* • To determine the progression-free survival of the combination of SABR and ipilimumab in patients with oligometastatic melanoma using mWHO criteria *Secondary and Correlative Objectives:* • To determine the progression-free survival of the combination of SABR and ipilimumab in patients with oligometastatic melanoma using irRC criteria • To evaluate the tolerability and safety of the combination • To evaluate of response rate based on mWHO & irRC criteria • To evaluate the local control rate • To evaluate the overall survival rate • To determine the effect of SABR and ipilimumab on changes in blood and serum markers: absolute lymphocyte count, T-cell activation markers, T-cell suppression markers, T-helper cells and related cytokines, T-reg markers, co-stimulatory molecules, and serum cytokines • To determine the association between response, progression-free survival and genomic DNA mutations in key melanoma genes and tumor antigen expression
Number of Subjects	32

Diagnosis and Main Inclusion Criteria	Male and female patients ≥ 18 years old with Stage IV melanoma *Key Inclusion Criteria:* • Confirmed melanoma with metastatic disease confined to an area amenable to SABR (lung, liver, bone, brain, adrenal, nodal station outside the regional lymph drainage of the primary) • 1-3 sites of metastatic disease to be targeted by SABR • Normal end organ function • Measurable disease by CT • ECOG PS of 0 - 2
Study Product, Dose, Route, Regimen	Ipilimumab will be administered on week 1 at a dose of 3 mg/kg. Subsequent cycles of ipilimumab will be given every three weeks (week 4, 7, & 10). SABR will be delivered between the second and third doses of ipilimumab(week 5-6) using the following suggested schedules: 18 Gy x 3 to lung, 10 Gy x 5 to liver, 6 Gy x 6 to nodal stations, 12 Gy x 3 to adrenal, 18 Gy x 1 to bone, and 24 Gy x 1, 18 Gy x 1, 15 Gy x 1 to < 2.0 cm, 2.0-3.0 cm, and >3 cm brain metastases, respectively. Duration of therapy: Patients will receive at least 12 weeks of therapy and will be observed for toxicity for 90 days after the last ipilimumab infusion. Patients will remain on study until evidence of progression or death.
Duration of administration	12 weeks
Reference therapy	NA

Statistical Methodology	Overall, this study will require 32 evaluable patients. We estimate that we will accrue 1-2 patients per month. Thus, the minimum study duration will be 16 months and the maximum is 32 months. Current literature and experience with maintenance therapy in this patient population shows that we can expect that this treatment regimen will not be considered promising in this patient population if at most 15% of patients are progression-free and alive at 6 months. For this agent to be considered promising in this patient population, we would expect an improvement in the 6-month PFS rate to at least 35% with this regimen in this patient population. Constraining the Type I and II error rates to 10% each, a 2-stage phase II Simon minimax study design will require 32 evaluable patients to test these hypotheses regarding the 6-month PFS rate with ipilimumab when given in combination with the stereotactic ablative radiation therapy in this patient population.

1.0 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Specific Aims

For nearly 30 years melanoma has been treated with chemotherapy agents like dacarbazine with a very modest benefit. A relative revolution in the treatment options for patients with metastatic melanoma has occurred over the last several years as promising targeted agents and immunotherapies have shown impressive disease stabilization rates. In order to turn impressive disease stabilization rates into actual long term disease control, additional therapeutic advances are needed. The immunotherapy agent ipilimumab is an exciting new agent which is being tested in a host of settings in melanoma to determine how to achieve a maximum benefit in disease control. We aim to improve the exciting advances in melanoma care afforded by ipilimumab by enhancing response rates and disease control with an aggressive local treatment like SABR (Stereotactic Ablative Radiation Therapy). This is important because overall response rates for melanoma immunotherapy remain low in metastatic disease and disease control rates stand at between 20 and 35% with overall survival measured in months[1].

The objectives of this study are:

Primary Objectives:

- To evaluate the 6-month progression-free survival of the combination of SABR and 3 mg/kg ipilimumab in patients with oligometastatic melanoma using mWHO criteria

Secondary Objectives:

- To evaluate the 6-month progression-free survival of the combination of SABR and 3 mg/kg ipilimumab in patients with oligometastatic melanoma using irRC criteria
- To evaluate the tolerability and safety of the combination
- To evaluate the response rate based on mWHO & irRC criteria[2]
- To evaluate the local control rate
- To evaluate the overall survival rate

Correlative Objectives:

- To determine the effect of SABR and ipilimumab on changes in blood and serum markers: absolute lymphocyte count, T-cell activation markers, T-cell suppression markers, T-helper cells and related cytokines, T-reg markers, co-stimulatory molecules, and serum cytokines

- To determine the association between response, progression-free survival and genomic DNA mutations in key melanoma genes and tumor antigen expression

1.2 Background and Rationale

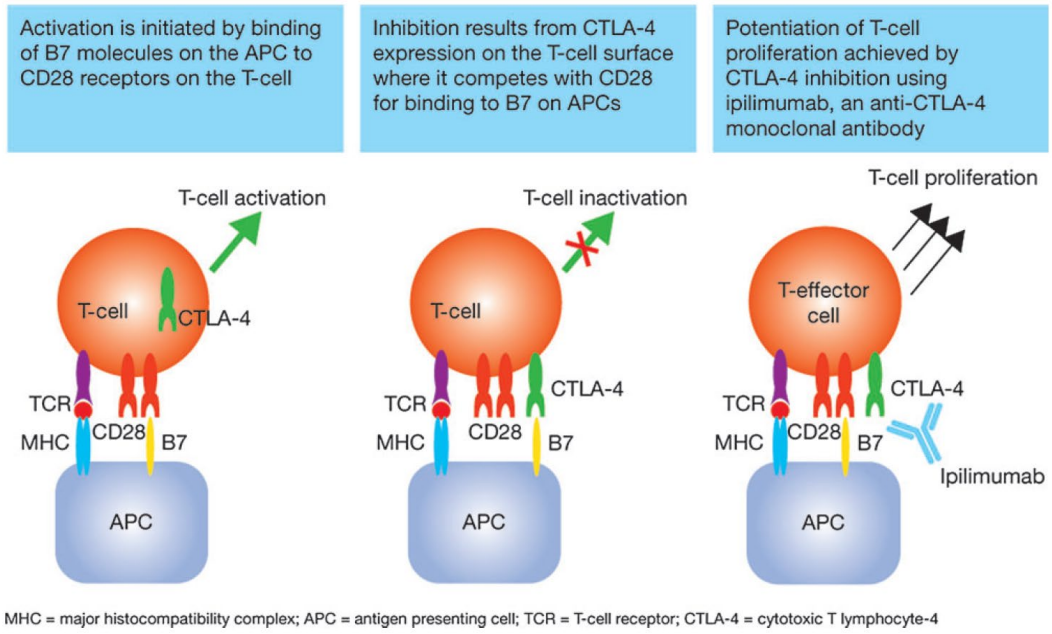
The regulatory pathways that limit the immune systems surveillance and response to melanoma are becoming increasingly well characterized. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is molecule with a checkpoint function that down-regulates pathways of T-cell activation[3]. Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks CTLA-4, and thereby promotes antitumor immunity[4-5]. Ipilimumab has shown impressive activity in patients with metastatic melanoma when it has been used as monotherapy in phase 2 studies[6-8] and a pivotal, recently reported phase III study[1]. This study evaluated whether ipilimumab with or without the gp100 vaccine improves overall survival, as compared with gp100 alone, among patients with metastatic melanoma who had undergone previous treatment. Ipilimumab was dosed at 3 mg/kg body weight. The median overall survival was 10 months for patients treated with ipilimumab and 6.4 months for the gp100 vaccine alone. Ipilimumab-treated patients had an 11% overall response rate and a 28% disease control rate. Ipilimumab was granted FDA approval for the treatment of metastatic melanoma in 2011 based largely on the survival benefit found by this trial.

1.2.1. The role of CTLA-4 and ipilimumab in melanoma

Activated T-cells and antibodies targeting tumor-associated antigens (TAAs) have commonly been detected in blood from patients with various types of cancer[9] supporting an active role for a host immune response against cancers. In melanoma, T-cell infiltrates in primary melanoma have prognostic significance[10], and T-cell infiltrates within regional nodal metastases predict benefit in patients treated with neoadjuvant interferon-α-2b therapy[11-12].

Two signals are required for full T-cell activation [13-14]. The first is initiated by T-cell receptor binding to TAAs presented by antigen presenting cells (APCs) via major histocompatibility complexes I and II. The second signal is launched when the principal co-stimulatory receptor on the T cell, CD28, binds to B7 ligand subtypes CD80 and CD86 on the APC. The resulting dual signaling induces cytokine release and T-cell proliferation which triggers and then amplifies the immune response. In response to T-cell activation, CTLA-4 is upregulated and competes with CD28 for CD80 and CD86 binding on APCs but with significantly higher affinity, therefore downregulating the T cell response (Fig. 1)[14]. CTLA-4, therefore, downregulates T-cell responses and APC function, resulting in a decreased immune response to TAAs and immune tolerance [13, 15]. CTLA-4 signaling contributes to the immunosuppressive function of regulatory T cells [16]. CTLA-4 is the main negative regulator of T-cell-mediated antitumor immune responses and therefore represents a critical immunity checkpoint, controlling both the duration and the intensity of an immune response [13, 15, 17].

Figure 1.1. Ipilimumab mechanism of action [14].



MHC = major histocompatibility complex; APC = antigen presenting cell; TCR = T-cell receptor; CTLA-4 = cytotoxic T lymphocyte-4

Ipilimumab (Yervoy, BMS-734016, MDX-010, MDX-CTLA4 Bristol-Myers Squibb) is a fully human, antagonistic monoclonal antibody directed against CTLA-4[18]. It promotes durable objective responses in patients with metastatic melanoma[1, 19]. It is approved by FDA to treat patients with unresectable or metastatic melanoma.

The safety and efficacy of Ipilimumab were investigated in a randomized (3:1:1), double-blind, double-dummy study that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin [1]. Of these 676 patients, 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 patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded patients 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 four 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. Patients 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 patients, 61%, 59%, and 54% in the Ipilimumab +gp100, Ipilimumab, and gp100 arms, respectively, were men. Twenty-nine 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 percent of patients randomized to either Ipilimumab-containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

1.2.2. The role of radiation therapy in melanoma

Historically radiation therapy has played several important roles in the management of melanoma: definitive treatment of primary lesions in patients too frail to undergo resection, palliative treatment of distant metastatic lesions and local recurrences, elective treatment of regional nodes at high risk for subclinical disease, and adjuvant treatment after resection of the primary lesion or metastatic regional nodes. It is estimated that radiation therapy is indicated in at least 23% of melanoma patients, though this modality is frequently under utilized[20]. The under utilization of radiation therapy occurs, in part, because of the long-held belief that melanoma is a radioresistant malignancy. *In vitro* studies have demonstrated a wide shoulder on the cell survival curve for many melanoma cell lines which suggests that melanoma has a large capacity for repair of sublethal damage. One way to overcome melanoma's intrinsic ability to repair sublethal damage is to deliver high-dose fractions of radiation therapy. In the past the potential enhancement of cell kill using high-dose fractionation had to be weighed against potential increases in late normal tissue complications.

The immune system plays a complex role in cancer control, and emerging evidence suggests that even in cell lines that in vitro are relatively radioresistant in vivo are sensitive due to the supportive anti-tumor effects of the immune system[21]. Various mechanisms of action have been postulated including increased T cell infiltration after in vivo radiation therapy, increased TNF alpha[22], induction of IL-1 alpha[23], and induction of IL-6[23].

1.2.3 The role of SABR in melanoma:

SABR is an advanced radiation therapy technique which delivers a high dose of photon-based radiation therapy to a tumor target with a high degree of conformality, thus minimizing the dose to nearby healthy tissues. SABR uses image-guided radiation therapy techniques like daily pretreatment kilovoltage or megavoltage CT scans and various forms of motion management to deliver high doses of radiation therapy to a tumor target in 1-5 total ablative treatments. SABR has become an exciting byproduct of recent advances in linear accelerator design and improvements in the physics of motion management. Most large cancer centers now have a robust experience treating brain, lung, liver, and skeletal metastases with SABR. Indeed, the local control rates from SABR to metastases in the lung has been so exciting that several of national clinical trials are

now enrolling or in development to compare the efficacy of SABR to that of invasive surgical resection (RTOG 1021)[24-25].

SABR was first applied to melanoma metastases to the vertebral bodies and brain with encouraging outcomes[26-29]. Aggressive targeting of individual melanoma sites of metastasis via SABR to the lungs and liver has been reported by Stinauer who treated 28 metastatic lesions in 17 patients using a SABR regimen of 40-50 Gy in 5 total fractions or 42-60 Gy in 3 total fractions[30]. The local control of metastases treated was 88% at 18 months and the median overall survival was 22.2 months.

The importance of aggressive local disease control and its ability to improve survival in melanoma was recently highlighted by the SWOG 9430 trial[31]. This phase II trial in 77 patients with oligometastatic melanoma examined the value of an attempted complete surgical resection of all sites of disease. They found a median overall survival of 21 months compared with 6.2 months in patients involved in cooperative group systemic therapy alone trials. Likewise, they found a median relapse-free survival of 5 months compared with the historical baseline of 1.7 months on cooperative group systemic agent alone trials. This trial suggests that aggressive treatment of oligometastatic disease may prolong survival. The potential advantages of using SABR as the local control method are that SABR is non-invasive and requires minimal recovery time.

1.2.4 The potential synergism of ipilimumab and SABR:

Ipilimumab and SABR are a particularly intriguing pair for concurrent treatment and potential synergism of effect. The underlying hypothesis is that radiation therapy, particularly radiation therapy using high doses per fraction, causes uncontrolled melanoma cell death and causes additional antigens to be presented in per-tumoral tissue during the uncontrolled cell death. The additional antigen presentation enhances the effect of immunotherapies like ipilimumab. Radiation therapy clearly affects various aspects of the immune system: a recent high profile publication[32] highlighted the induction of the abscopal effect by radiation therapy and conversely, the importance of immune function on the ablative properties of high dose per fraction radiation therapy[33]. Subsequently, a number of publications have hypothesized a role for the combination of immune-modulating drugs like ipilimumab and radiation therapy[34-40].

1.2.5 Hypothesis:

We hypothesize that hypo-fractionated radiation therapy causes aberrant cell death processes which may result in additional antigen presentation. When combined with ipilimumab the additional antigen presentation may incite a more robust immune response.

1.3 Investigational Agent

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1κ) specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells. The proposed mechanism of action for ipilimumab is T-cell potentiation through interference of the interaction of CTLA-4 with B7 (CD80 or CD86) molecules on antigen presenting cells, with subsequent blockade of the inhibitory function of CTLA-4. Ipilimumab consists of four polypeptide chains; two identical heavy chains primarily consisting of 447 amino acids each with two identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds.

1.4 Preclinical Data

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.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future ipilimumab clinical studies. Biochemical, immunologic and *in vivo* preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

1.4.2 Pre-Clinical Toxicology of Ipilimumab

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 Preclinical data on combination with radiation therapy

Currently, there is no data on the combination of Ipilimumab with radiation in preclinical studies. A study evaluated the efficacy of a different CTLA-4 antibody (9H10) in combination of radiation treatment [41]. Radiation treatment consists of 12 Gy in two daily fractions. The CTLA-4 antibody was administered 1, 4 and 7 days after radiation treatment. Combination treatment showed significant inhibition of the tumor growth compared to radiation treatment combined with control antibody treatment [41].

1.5 Clinical Data to Date

1.5.1 Human 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 mg/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).[16,17,18] 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.

1.5.2 Clinical Safety with Ipilimumab

Overview of Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or

experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

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

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

Table 1 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the ipilimumab-containing arms and with at least 5% increased

incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3–5 events.

Table 1: Selected Adverse Reactions in MDX010-20

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

- [a] Incidences presented in this table are based on reports of adverse events regardless of causality.
- Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

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

Table 2: Severe to Fatal Immune-mediated Adverse Reactions in MDX010-20

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

– [a] Including fatal outcome

- [b] Including intestinal perforation
- [c] Underlying etiology not established
- Source: Yervoy Prescribing Information, Bristol-Myers Squibb, March 2011.

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

Immunogenicity

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.

Pregnancy Outcomes

Based on animal data, ipilimumab may cause fetal harm. The use of ipilimumab during human pregnancy has not been formally studied in clinical trials. There have been 7 known pregnancies during ipilimumab treatment: in 3 female subjects and in the partners of 4 male study subjects. Two (2) of the 3 female pregnancies ended with elected terminations. The third female subject had a history of 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.

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.

1.5.3 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 previously-treated, locally advanced/metastatic melanoma), which led to approval of ipilimumab by the FDA for the treatment of unresectable or metastatic melanoma. In study CA184024, the addition of 10 mg/kg ipilimumab to dacarbazine led

to a prolongation of overall survival in patients with previously untreated melanoma and was feasible with an acceptable safety profile.

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

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

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

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

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

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

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

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

Hence the appearance of new lesions in and of themselves may not necessarily constitute progressive disease. The immune-related response criteria (irRC) were

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

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

The design and results of the MDX010-20 trial are discussed in Section 1.2.1.

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

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized

to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg/kg or placebo cycles 1-4, and as maintenance after completion of chemotherapy.

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

Table 6: CA184024 Baseline Characteristics

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

Table 6: CA184024 Baseline Characteristics

	Ipilimumab + DTIC n = 250	Placebo + DTIC n = 252
Prior adjuvant therapy (%)	26.4	26.6
Prior therapy for advanced disease (%)	0	0

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

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

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

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

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

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

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

Table 7: CA184024 Tumor Response

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

1.6 Overall Risk/Benefit Assessment

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

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

Immune-related 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.

Hypo-fractionated radiation therapy is currently used for many indications including treating solitary, oligometastatic, or oligo-progressive disease in a number of cancers. Indeed, hypo-fractionated radiation therapy delivered with stereotactic precision and on-board image guidance allows ablative doses of radiation therapy to be delivered to masses in the brain, lung, liver, spine, and selected abdominal sites. One of the main obstacles to the success of immunotherapy is the fact that the immune system is tolerant to antigens on growing tumors. There is evidence that CTLA-4 blockade was effective when used in combination with radiation to produce granulocyte/macrophage colony-stimulation factor [41-42]. Combining CTLA-4 antibody with radiation treatment showed to be superior to radiation treatment alone in a preclinical tumor model [41]. In this study, we will use the standard doses for SBRT. We hypothesize that hypo-fractionated radiation therapy causes aberrant cell death processes which may result in additional antigen presentation. When combined with ipilimumab the additional antigen presentation may incite a more robust immune response. Therefore, the overall risk-benefit ratio for

patients entering this protocol is therefore at least comparable to and possibly better than alternative options.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine the progression-free survival of patients with oligometastatic melanoma treated with the combination of stereotactic ablative radiation therapy (SABR) and ipilimumab in patients with oligometastatic melanoma using mWHO criteria

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the 6-month progression-free survival of the combination of SABR and 3 mg/kg ipilimumab in patients with oligometastatic melanoma using irRC criteria
- To evaluate the tolerability and safety of the combination
- To evaluate the response rate based on mWHO & irRC criteria[2]
- To evaluate the local control rate
- To evaluate the overall survival rate

2.3 **Exploratory/Correlative Objectives**:

The exploratory objectives of this study are as follows:

- Evaluate changes in blood and serum markers: absolute lymphocyte count, T-cell activation markers, T-cell suppression markers, T-helper cells and related cytokines, T-reg markers, co-stimulatory molecules, and serum cytokines when SABR is added to the ipilimumab regimen
- Evaluate genomic DNA mutations in key melanoma genes and their correlation with response, progression-free survival, and overall survival

3.0 STUDY DESIGN

3.1 General Design

Phase II, single-arm, open label, non-randomized study with ipilimumab and SABR as outlined in the treatment plan. Patients with oligometastatic melanoma who are treatment naïve or previously treated with a non-ipilimumab regimen will be treated with ipilimumab 3 mg/kg. Each ipilimumab cycle is 3 weeks (21 days) with treatment administered on day 1. SABR to 1-3 metastatic sites will be delivered in-between the second and third ipilimumab doses. All patients are expected to complete four cycles of ipilimumab. Response will be assessed with contrasted CT imaging prior to ipilimumab therapy and after the 4th ipilimumab treatment using mWHO & irRC criteria[2]. Correlative studies will focus on identifying changes in blood and serum T-cell activation and expression markers when SABR is added to the ipilimumab regimen and to evaluate the effect of key melanoma genomic DNA mutations on outcomes like response, progression-free survival and overall survival with this regimen.

The study will consist of the following schedule:

3.1.1 Screening

- Assessment of the subject's eligibility to participate as determined by the inclusion/exclusion criteria.

3.1.2 Treatment

- The recommended dose of ipilimumab as a single agent is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses, as tolerated.

- Laboratory evaluations should be performed and the results examined before administration of each ipilimumab dose.

- As durable disease stabilization and/or objective tumor response can be seen after early progression before Week 12, it is recommended that, in the absence of dose-limiting toxicities (eg, serious immune-mediated adverse reactions), all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.

- All subjects who are treated with ipilimumab including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression during the treatment period, should obtain a 12-week tumor assessment.

- Based on clinical experience in the ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the Week 12 or later tumor assessments:

The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.

As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance, even in the presence of new lesions.

Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

In our study we propose to evaluate a combination of ipilimumab and SABR in patients with oligometastatic melanoma in a phase II trial.

The study will consist of the following schedule: ipilimumab will be administered on week 1 at a dose of 3 mg/kg.

Subsequent cycles of ipilimumab will be given every three weeks (week 4, 7, & 10).

SABR will be delivered between the second and third doses of ipilimumab (usually week 5-6 if no delays for ipilimumab toxicity) using the following suggested schedules: 18 Gy x 3 to peripheral lung, 10 Gy x 5 to central lung, 10 Gy x 5 to liver, 6 Gy x 5 to nodal stations, 12 Gy x 3 to adrenal, 24 Gy x 1 brain < 2 cm, 18 Gy x 1 brain 2-3 cm, and 15 Gy x 1 brain > 3 cm, 16-18 Gy x 1 to vertebral sites.

Duration of therapy: Patients will receive at least 12 weeks of therapy and will be observed for toxicity for 90 days after the last ipilimumab infusion. Patients will remain on study until evidence of progression by both mWHO and irRC or death. Patients in whom new lesions develp or baseline lesions grow will receive additional ipilimumab treatments to complete induction therapy.

3.1.3 Reinduction

- Patients with stable disease for 3 months' duration after completion of ipilimumab therapy (usually week 12) will be offered re-induction ipilimumab at 3 mg/kg at the treating physicians discretion[1].

- Patients with a confirmed partial or complete response after completion of ipilimumab therapy (usually week 12) will be offered re-induction ipilimumab at 3 mg/kg at the treating physicians discretion[1].

3.1.4 Follow-up

- Subjects who are no longer receiving ipilimumab because of unacceptable toxicity (refractory Grade > 3 immune-mediated adverse reactions) or due to investigator judgment are managed in follow-up. Efficacy assessments for these subjects during follow-up are as per the standard of care. Date of death is recorded.

- Subjects who discontinue ipilimumab treatments should be followed until death or the closure of the study (whichever is first).

- Subjects who are no longer receiving ipilimumab because of clinical progression and who have switched to alternative treatment are not followed formally except to record the date of death.

3.2 Primary Study Endpoints

- Rate of progression-free survival of ipilimumab and SABR in patients with oligometastatic melanoma as measured from the time of study enrollment until the first documented date of disease progression by mWHO criteria

3.3 Secondary Study Endpoints

- Rate of progression-free survival of ipilimumab and SABR in patients with oligometastatic melanoma as measured from the time of study enrollment until the first documented date of disease progression by irRC criteria

- Frequency of grade 3 and grade 4 toxicities according to CTCAE (Common Toxicity Criteria for Adverse Events) version 4

- Frequency of objective response rate, defined as complete response + partial response, measured by CT using modified World Health Organization (mWHO) criteria

- Frequency of objective response rate, defined using irRC

- Rate of local failure, as measured from the time of study enrollment until the first documented date of failure within the irradiated field

- Rate of overall survival, as measured from the time of study enrollment until the time of death

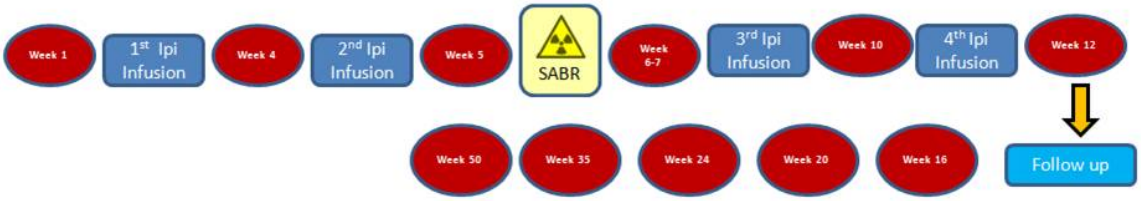
3.4 Correlative/Exploratory Study Endpoints

Blood and tissue samples will be collected for research purposes. Planned studies include exploration of certain gene mutations and serum markers as predictors of response to ipilimumab treatment. Proteomics expression patterns will be used to

determine if they are a prognostic/predictive marker for treatment response. Research lab studies will also evaluate if primary tumor cells and melanoma stem like cells can be isolated from the tissues using our in-house laboratory techniques. These cells may be transitioned to long-term cell lines for further research.

Sample collection scheme

Blood and serum samples for correlative analysis will be collected pre-treatment, prior to ipilimumab infusions and after completion of the treatment portion of the trial. The various time points for blood draw are shown in red circles with timelines. Tissue samples will also be collected in the event that re-biopsy or surgical resection is clinically indicated.



The Week 6-7 blood draw illustrated above will take place prior to the 3rd ipilimumab infusion and is hereafter referred to as the "Week 7" blood draw.

Blood and serum markers: We propose to determine the expression levels of various seromic proteins and cell surface markers. The marker proposed includes:

Blood markers:

- Change in Absolute Lymphocyte count (ALC) and LDH.

T cell markers:

- Change in Immune regulation after Ipilumimab infusion by measuring CD152 (CTLA-4) and CD28 (Co-stimulatory signal) by FACS.
- Change in T cell activation markers CD3, CD4, CD8, HLA-DR, ICOS, C11b, CD69, CD137, CD154, CXCL16 by FACS.
- Change in T cell suppressor – Myeloid derived suppressor cells CD14 and HLA-DR.

- Change in T helper 17 (Th17) cells and related cytokines IL-17 and IL-22 by intracellular cytokine staining and FACS- Change in Regulatory T cells 'Tregs' CD4, CD25/LAP, and CD127 by FACS and IDO by mass spectrometer

- Change in B-7 family costimulatory molecules: CD80(B7-1), CD86(B7-2) by FACS.

Cytokine Markers:

- Change in cytokine milieu as assessed by the Bioplex Assays using serum samples: Human 8-plex assay; IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, TNF-α and Human Th17 cytokine panel; IL-1β, IL-4, IL-6, IL-10, IL-17A , IL-17F, IL-21, IL-22 , IL-23 , IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α, IL-17A/F by ELISA or FACS.

Tissue sections: Genomic DNA from the tissue sections will be isolated along with matched blood samples and will be used for the following analysis;

- Ratio of effector and regulatory T cells "Teff/Treg" by correlating with the levels of FoxP3 and IDO by IHC and RT-QPCR respectively in tissues when available.

- Rate of mutation and correlation to outcomes of key melanoma genes BRAF, NRAS, KIT, CDKN2A, PIK3CA, PTEN, TP53, MEK, EGFR, Akt, using castPCR technique.

- The tissue microarray (TMAs) obtained after Dermatopathologist selected/ reviewed area will be used for fluorescence based Immunohistochemistry and the expression intensity of images will be scored using an automated system.

- Change in tumor antigens over time such as Melan-A, NY-ESO-1, MAGE, MART-1, gp-100, and tyrosinase. The co-localization and subcellular localization / abundance will also be determined. We will also include ELISA based assay to estimate the antibody required for neutralizing melanoma antigens in serum.

4.0 SUBJECT SELECTION AND WITHDRAWAL CRITERIA

For entry into the study, the following criteria MUST be met. Any exceptions from the protocol-specific selection criteria must be approved by the Principal Investigator and/or the Institutional Review Board (IRB) before enrollment.

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations will be reviewed by the Principal Investigator prior to enrollment, to verify that all inclusion and exclusion criteria have been satisfied. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion criteria

1) Willing and able to give written informed consent.
2) ≥ 18 years of age
3) ECOG Performance Status 0-2 (see Appendix I)
4) Histologic diagnosis of melanoma with metastatic disease to a visceral organ (lung, liver, brain, adrenal, nodal station outside the regional lymph drainage of the primary, vertebral bodies)
5) 1-3 sites of metastatic disease able to be targeted by SABR
6) Required values for initial laboratory tests:

- WBC ≥ 2000/uL
- ANC ≥ 1000/uL
- Platelets ≥ 75 x 10^3/uL
- Hemoglobin ≥ 9 g/dL (≥ 80 g/L; may be transfused)
- Creatinine ≤ 2.0 x ULN
- AST/ALT ≤ 2.5 x ULN for patients without liver metastasis,
  ≤ 5 times for liver metastases
- Bilirubin ≤ 2.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
- No active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
- Negative Pregnancy test at screening
- WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 3 days before the start of ipilimumab.

7.) Women of childbearing potential (WOCBP) and male subjects of fathering potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 3 months after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as:

- Amenorrhea ≥ 12 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 (eg, vasectomy) should be considered to be of childbearing potential.

Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 3 months after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1) Any other malignancy from which the patient has been disease-free for less than 3 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma *in situ* of the cervix.

2) Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis).

3) Any underlying medical or psychiatric condition, which in the opinion of the

investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.

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4) Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).

5) Concomitant therapy with any of the following: IL-2, interferon, other non-study immunotherapy regimens, cytotoxic chemotherapy, other investigation therapies

6) Concomitant therapy with immune-suppressants or chronic use of systemic corticosteroids.

7) Must be off prior systemic therapies for 2 weeks prior to enrollment. Patients that have been previously treated with systemic therapy adjuvantly or for metastatic disease remain eligible as long as they continue to meet all other eligibility criteria (oligometastatic, no visceral metastasis > 5 cm, eligible for SABR)

8) Prior radiation therapy that at the treating physician's discretion makes SABR unsafe

9) No clinically significant evidence of pleural effusion or ascites

10) Congestive heart failure > class II NYHA or unstable angina

11) Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy

12) Major surgery, open biopsy or significant traumatic injury within 2 weeks of first dose of study drug

13) A visceral metastasis greater than 8 cm

14) A visceral metastasis that due to its location cannot be safely treated with SABR

15) Women of childbearing potential (WOCBP), defined above in Section 4.1, who:
    a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 3 months after cessation of study drug, or
    b. have a positive pregnancy test at baseline, or
    c. are pregnant or breastfeeding.

16) Male subjects of reproductive potential who are unwilling or unable to use an acceptable method of contraception with their female partners for their entire study

period and for at least 3 months after cessation of study drug.

17) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness.

18) Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO)

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. All WOCBP MUST have a negative pregnancy test before first receiving ipilimumab. If the pregnancy test is positive, the patient must not receive ipilimumab and must not be enrolled in the study.

4.3 Gender/Minority/Pediatric Inclusion for Research

This study includes both genders and minority patients. Pediatric patients are excluded.

4.4 Subject Recruitment and Screening

Patients who are 18 year of age or older with oligometastatic melanoma are eligible for this study. Patients can be recruited from PI or co-investigators' clinical practices. Potential study subject should be notified to PI and study designated research nurse/research associate. Appropriate laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria will be ordered through the recruiting physician. PI of the study will screen and determine the final eligibility of the subject for enrollment.

4.5 Early Withdrawal of Subjects

4.5.1 <u>When and How to Withdraw Subjects</u>

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

1. Intercurrent illness
2. Occurrence of an unacceptable adverse event
3. Patient request
4. Protocol violations
5. Non-compliance
6. Administrative reasons
7. Failure to return for follow-up

8. General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

According to FDA regulations, when a subject withdraws from the study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

A subject who is withdrawing needs to state whether he/she wishes to provide continued follow-up and further data collection subsequent to withdrawal from the interventional portion of the study.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the subject will continue follow up visit and evaluation per the protocol.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, study data related to the subject collected prior to the subject's withdrawal from the study will be included in the study analysis.

5.0 STUDY DRUG

Ipilimumab

5.1 Dose Calculations

Each patient will receive ipilimumab 3 mg/kg infusions over 90 minutes (not bolus or IV push) on weeks 1, 4, 7, & 10.

Calculate **Total Dose** as follows:

Patient body weight in kg x (3) mg = 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 weighing 114 kg (250 lb) would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 342 mL (342 mg ÷ 1 mg/mL = 342 mL) at a rate of approximately 2.5 mL/min (342 mL ÷ 2.5 mL/min) in 137 minutes.

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). The maximum dose of ipilimumab is 400 mg. Therefore, patients ≥ 133 kg should not receive a dose > 400 mg.

5.2 Storage, Preparation, and Administration

Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

Do not shake product.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced

discoloration (solution may have pale yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.

Withdraw the required volume of ipilimumab and transfer into an intravenous bag.

Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.

Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).

Discard partially used vials or empty vials of ipilimumab.

Administration Instructions

Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.

Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

See the current Investigator Brochure for additional information on allowable filter types. The infusion must be completed in 90 minutes with a 10 ml normal saline flush at the end.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only.

5.3 Dose Modification

Ipilimumab Dose Skipping Rule

Decisions to skip an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be skipped or discontinued if the subject experiences at least one adverse event, specified below, considered by the investigator to be **"possibly," probably," or "certainly" related to ipilimumab**

treatment. The investigator should contact BMS for any adverse event that will prompt a skipped dose or discontinuation of ipilimumab.

The following criteria will be used to determine dose skipping, restarting doses, or discontinuing ipilimumab.

It may be necessary to skip study drug dosing for the following related adverse event(s):

Any ≥ Grade 2 non-skin related adverse event (including immune-mediated adverse reactions), except for laboratory abnormalities

Any ≥ Grade 3 laboratory abnormality

Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.

It is necessary to skip study drug dosing for the following adverse events:

Any ≥ Grade 3 skin related adverse event regardless of causality.

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 2 weeks of planned dose administration:

If the *adverse event has resolved,* restart ipilimumab dosing at the next scheduled time point per protocol.

If the adverse event has not resolved in the protocol-specified dosing window (3 weeks [±3 days]), the next scheduled dose will be skipped and dosing will be resumed at the subsequently scheduled dose.

If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

5.4 Discontinuation of Study Therapy

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

Withdrawal of informed consent (subject's decision to withdraw for any reason)

Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject

Pregnancy

- All WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.

- The investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.

Termination of the study by Bristol-Myers Squibb (BMS).

Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

Permanent Discontinuation of Ipilimumab

Permanent Discontinuation for Related Adverse Events

Permanently discontinue ipilimumab for any of the following:

Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Severe or life-threatening adverse reactions, including any of the following:

- Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for

intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

– Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal

– Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations

– Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis

– Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, hypophysitis)

– Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

– 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.

– The development of progression as defined in the irRC[2] as at least a 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart and/or clinical deterioration of

subject's condition such that further benefit from ipilimumab dosing is unlikely or requires a change of therapy at the treating physician's discretion.

Please refer to the IB for specific treatment algorithms.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity >/= Grade 3 regardless of causality
- Any >/= Grade 3 treatment related sensory neurologic toxicity

Please refer to the IB for specific treatment algorithms.

Exceptions to Permanent Discontinuation

Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.

Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.

Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:

- Ocular toxicity that has responded to topical therapy.
- Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

5.5 Immune-Related Adverse Events (irAEs) Reactions and Immune-mediated Adverse Reactions: 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 immune-mediated adverse reactions, noted in previous ipilimumab studies.

For the purposes of this study, an immune-related adverse reaction is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an immune-related adverse reactions. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form. Another term for an irAE is an immune-mediate adverse reaction, as it is termed in the Ipilimumab US Prescribing Information. Both terms may be used in this protocol document.

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

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

Specific treatment algorithms for immune-mediated adverse reactions adverse events are included as appendices in the IB.

Other Guidance

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 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.

- Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.

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

- Interrupt ipilimumab.

- Administer diphenhydramine 50 mg IV.

- Monitor patient closely until resolution of symptoms.

- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.

- Resume ipilimumab infusion after recovery of symptoms.

- At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*

- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.

- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and

acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.

– At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

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

– Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.

– Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with 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).

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.

Monitoring and Management of Immune-mediated Adverse Reactions

Immune-mediated Enterocolitis

Patients will be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients,

rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue ipilimumab in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. 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. For steroid-refractory colitis infliximab 5 mg/kg IV or cyclosporine 2 mg/kg IV for 7 days are recommended[43].

Withhold ipilimumab dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than one week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent.

Immune-mediated Hepatitis

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of ipilimumab. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue ipilimumab in patients with Grade 3–5 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold ipilimumab in patients with Grade 2 hepatotoxicity.

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.

Permanently discontinue ipilimumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at

least 1 month. Withhold ipilimumab dosing in patients with moderate to severe signs and symptoms.

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

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 syndromes. 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).

Immune-mediated Endocrinopathies

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Withhold ipilimumab dosing in symptomatic patients. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in previous studies: 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.

Liver Function Test (LFT) Assessments Required Before Administration of Ipilimumab

Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed at local or central labs within 3 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: $\leq$ 2.5 x ULN for AST, ALT and $\leq$ 1.5 x ULN for T. bilirubin unless liver metastases are present in which case LFT $\leq$ 5 x ULN for AST, ALT and T. bilirubin $\leq$ 3.0 x ULN) prior to dosing.

If during the course of treatment abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm section of the ipilimumab Investigators.

5.6 Prohibited and Restricted Therapies During the Study

Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre- and post-dosing with ipilimumab. Concomitant systemic or local anti-cancer

medications or treatments are prohibited in this study while receiving ipilimumab 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
- Anti PD-1 or anti PD-L1 antibodies
- CD137 agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- 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).

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.

5.7 Method for Assigning Subjects to Treatment Groups

This is an open label phase 2 study. There is no randomization. Patients will all receive ipilimumab 3 mg/kg for 4 doses 3 weeks apart. Between the second and third dose SABR will be used to oligometastatic sites.

5.8 Subject Compliance Monitoring

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. The radiation treatment record will be reviewed and recorded.

5.9 Prior and Concomitant Therapy

No other concomitant chemotherapy or systemic anti-melanoma therapy is allowed for the study.

6.0 STUDY PROCEDURES

6.1 Treatment overview

We will evaluate the combination of ipilimumab and SABR in patients with oligometastatic melanoma in this phase II trial.

The study will consist of the following schedule: ipilimumab will be administered on week 1 at a dose of 3 mg/kg.

Subsequent cycles of ipilimumab will be given every three weeks (week 4, 7, & 10).

SABR will be delivered between the second and third doses of ipilimumab (week 5-6) using the following suggested schedules: 18 Gy x 3 to lung, 10 Gy x 5 to liver, 6 Gy x 6 to nodal stations, 12 Gy x 3 to adrenal, 18 Gy x 1 to bone, and 24 Gy x 1, 18 Gy x 1, 15 Gy x 1 to < 2.0 cm, 2.0-3.0 cm, and >3 cm brain metastases, respectively.

Duration of therapy: Patients will receive at least 12 weeks of therapy and will be observed for toxicity for 90 days after the last ipilimumab infusion. Patients will remain on study until evidence of progression or death. Patients who meet criteria for reinduction therapy remain on study and re-induction is recommended if the criteria in Section 3.1.3 are met.

6.2 Screening

Within four weeks of starting treatment, patients will have baseline hematologic studies including complete blood count plus differential, blood chemistry studies including chemistries, hepatic and renal function tests, thyroid and ACTH levels and a pregnancy test. Women of childbearing potential will have a pregnancy test within 3 days of starting treatment.

Within four weeks of starting treatment, patients will have CT of the chest, abdomen, and pelvis and/or PET/CT scan.

6.3. Stereotactic Ablative Radiation Therapy

6.3.1 Radiation Therapy

SABR has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic

Radiology and Oncology. This protocol will respect that guideline. The term stereotactic for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable "fiducial" markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radiopaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). Metallic "seeds" placed within the tumor will be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

6.3.2 Fractionation, Total Dose and Radiation Therapy Planning

Megavoltage external beam photon radiation therapy will be used delivered by a linear accelerator generating 6 MV photons or in the case of SRS to the brain a Gamma Knife. A CT simulation or MR simulation will be used for radiation therapy planning. During simulation where appropriate a 4-D CT should be used to determine the motion of targeted metastases with respiration. Efforts to limit respiratory motion such as gated treatment, Active Breath Control systems, or abdominal compression should be used in order to minimize necessary GTV to ITV expansions.

6.3.3 Field Definition

Gross tumor volume (GTV) is defined as the full extent of the imaging abnormality.

ITV is defined as the GTV plus margin needed to account for physiologic motion as determined by the data acquired at the time of 4-D CT.

Clinical target volume (CTV) equals ITV in SABR.

The planning target volume (PTV1) includes the CTV plus a 0.5 cm margin for set-up error and/or patient motion. Exact margins will be left to the discretion of the treating radiation oncologist.

6.3.4 Dose Considerations

Lung SABR recommended doses: 18 Gy x 3 to peripheral lung masses, 10 Gy x 5 to central lung masses given 2 fractions per week

Liver SABR recommended doses: 10 Gy x 5 given 2-3 fractions per week

Nodal station SABR recommended doses: 6 Gy x 6 given 3 fractions per week

Adrenal SABR recommended doses: 12 Gy x 3,

Vertebral body SABR recommended doses: 16-18 Gy x 1 respecting normal tissue spinal cord constraints particularly no more than 10 Gy to 10% of cord volume

Brain parenchymal SABR recommended doses: 24 Gy x 1, 18 Gy x 1, 15 Gy x 1 to < 2.0 cm, 2.0-3.0 cm, and >3 cm brain metastases, respectively dosed to the 50-70% isodose line if using Gamma Knife SRS.

Fractionation: Treatment shall be given 2-3 days per week at the treating radiation oncologist's discretion.

Dose Homogeneity: The dose throughout the treatment volume will be within 10% of the prescribed dose. Wedges, compensation, and other methods of generating a uniform dose distribution are encouraged. IMRT can be used to shape dose around critical normal structures.

Isodose Plans: The isodose distribution for the composite plan shall be calculated. The prescription point and the outline or the tumor volume shall be shown.

Image guidance: Pre-treatment kilovoltage on board CT imaging will be done for localization, and shifts will be made as appropriate per the treating radiation oncologist.

Treatment Modification: Uninterrupted treatment is planned, and SABR fractions should occur during the period between the 2nd and 3rd doses of ipilimumab (generally weeks 5-6). SABR can be delayed at the physician's discretion if there is concern for overlapping toxicities with ipilimumab, but SABR should always be delivered between infusion 2 and infusion 3 of ipilimumab. The entire course of SABR should be delivered within the 3 week period between ipilimumab infusions, except in the case of a grade 3+ toxicity in the middle of the course of SABR. If a grade 3+ toxicity occurs during SABR which interrupts the delivery of SABR, then the final SABR fractions will be delivered after the toxicity returns to grade or lower with appropriate supportive care measures.

On Treatment Management: The patient will be examined at least once a week during the course of radiation therapy.

6.3.5 Dosimetry

3D Conformal Planning

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized.
For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3.5 cm when treating small lesions (see
above). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record. The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. The prescription dose will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hotspot" will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

Intensity Modulated Radiation Therapy (IMRT)

IMRT is allowed in this study. The NCI Guidelines for the Use of IMRT can be found on the RTOG homepage, http://www.rtog.org/. The use of IMRT in this study is at the discretion of the treating radiation oncologist. IMRT should be considered only when target coverage, OAR dose limits, or dose spillage
are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized (2-3 segments per beam should be adequate), and the

area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam's eye view).

6.4 Interruption and discontinuation

Treatment delays are occasionally encountered during radiation therapy due to logistic problems (e.g. machine break downs, patient transportation issues) or public holidays. If this occurs radiation therapy shall be completed as soon as possible.

6.5 Visit Schedule

6.5.1 Pre-Study Clinical Laboratory Tests and Procedures

Prior to study treatment each patient will have the following assessments.

Within 4 weeks of starting study treatment:

- Radiologic studies for baseline tumor measurements with CT or MRI scanning (PET/CT is optional)
- History and physical exam
- CBC
- CMP
- Thyroid function and ACTH
- Urinalysis
- Serum pregnancy test
- Blood collection for correlative endpoints

Within 3 days prior to first ipilimumab infusion

- **Urine or Serum pregnancy test for WOCBP**

6.5.2 On-Study Clinical Laboratory Tests and Procedures

Before ipilimumab infusion:

- Evaluation for adverse events
- CBC and CMP
- Blood collection for correlative endpoints (before 2nd and 3rd ipilimumab infusion, before initiation of SABR)

6.5.3 Follow-up Clinical Laboratory Tests and Procedures

Thirty days after 4th ipilimumab infusion (+/- 20 days) with the goal of 30 days for the first visit

- History and physical examination
- Evaluation for adverse events
- CBC and CMP

- Blood collection for correlative endpoints:Week 12, 16, 20, 24, 35, and 50 (+/-20 days

6.6 Study Procedures By Visit and Treatment Cycle

Note that results of all safety laboratory tests (that is, all chemistry and all hematology results) must be obtained and reviewed before ipilimumab administration, as applicable. All laboratory results must be within the established range before ipilimumab is administered. All induction period laboratory samples must be collected within a window of up to 4 weeks before administration of ipilimumab. Laboratory evaluations using a local laboratory must be performed and the result examined by the investigator before administration of each dose of ipilimumab.

6.6.1 Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

6.6.2 Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

6.7 Study Materials

Bristol-Myers Squibb (BMS) will provide ipilimumab at no cost for this study.

6.8 Safety Assessments

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of non-SAE or SAE from time of consent forward, up to and including follow-up visits, will be reported. See Section 8: Adverse Event Reporting.

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

6.9 Adverse events

The types of expected adverse events of SABR are directly related to the anatomical site being treated with SABR:

Lung SABR:

Expected acute toxicities- cough, dyspnea, fatigue

Possible sub-acute toxicities- radiation pneumonitis, rib fracture, chest wall pain

Liver SABR:

Expected acute toxicities- fatigue, diarrhea, increase in LFT's, nausea, vomiting

Possible sub-acute toxicities- chronic LFT elevation, gastric ulcer, duodenal ulcer, liver dysfunction

Spine SABR:

Expected acute toxicities- fatigue, nausea, vomiting, diarrhea

Possible sub-acute toxicities- radiation myelitis, vertebral fracture

Adrenal SABR:

Expected acute toxicities- fatigue, nausea, vomiting, diarrhea

Possible sub-acute toxicities- small bowel ulceration, small bowel obstruction

Nodal SABR:

Expected acute toxicities- fatigue, skin erythema, nausea, vomiting, diarrhea

Possible sub-acute toxicities- skin fibrosis, small bowel ulceration, small bowel obstruction

Brain stereotactic radiosurgery

Expected acute toxicities- headache, fatigue

Possible sub-acute toxicities- seizure, cerebral radionecrosis

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they

are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or CTCAE v4.0 criteria (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

6.10 Definition of Efficacy Assessments

- Rate of progression-free survival of ipilimumab and SABR in patients with oligometastatic melanoma as measured from the time of study enrollment until the first documented date of disease progression by both mWHO and irRC criteria.

- Frequency of grade 3 and grade 4 toxicities according to CTCAE (Common Toxicity Criteria for Adverse Events) version 4

- Frequency of objective response rate, defined as complete response + partial response, measured by mWHO criteria based on radiographic response rate will be determined based on re-staging CT of the chest, abdomen and pelvis

- Frequency of objective response rate, defined using the immune related response criteria (irRC) based on radiographic response rate will be determined based on re-staging CT of the chest, abdomen and pelvis

- Rate of local failure, as measured from the time of study enrollment until the first documented date of failure within the irradiated field

- Rate of overall survival, as measured from the time of study enrollment until the time of death

Biopsy, clinical evidence and radiographic evidence are all acceptable and will be used to document progression**.**

Overall survival: will be calculated as the time from entry on the study until the time of death.

Re-staging imaging with contrast-enhanced CT or MRI of the chest, abdomen, and pelvis will be performed before treatment, prior to 3rd ipilimumab infusion, 4 weeks after the final ipilimumab infusion (week 14 if there are no interruptions), and every 3 months for the first 2 years, then every 6 months during years 2-5.

The first re-staging scans after the week 14 imaging will be done at the 6 months from enrollment time point so that the endpoint of 6 month progression-free survival can be assessed.

All patients that have been treated on protocol with SABR and ipilimumab will have re-staging imaging even if they were taken off of protocol for adverse events after the SABR. Patients who do not have SABR due to adverse events from the first 2 infusions of ipilimumab are not required to complete re-staging imaging.

Patients who meet the criteria for Complete Response or Partial Response will have a re-imaging 4-weeks later to confirm the response.

6.10.1 Definition of Measurable/Non-Measurable and Index/Non-Index Lesions

Definitions of lesions are based on *mWHO criteria or immune-related response criteria (irRC)* in this study.

Definition of Measurable and Non-Measurable Lesions

Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.

Non-Measurable (evaluable) Lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
- All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment timepoints (see Section 5, Table 2). Extra

assessments may be performed, as clinically indicated, if there is a suspicion of progression.

Definition of Index/Non-Index Lesions

All measurable lesions, up to a maximum of **five lesions per organ** and **ten lesions in total,** should be identified as *index* lesions to be measured and recorded on the medical record at Screening. The *index* lesions should be representative of all involved organs. In addition, *index* lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the patient's tumor burden. At Screening, a sum of the products of diameters (SPD) for all *index* lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the *index* lesions at tumor assessment (TA).

Measurable lesions, other than *index* lesions, and all sites of non-measurable disease, will be identified as *non-index* lesions. *Non-index* lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the *index* lesions. In subsequent assessments, *non-index* lesions will be recorded as "stable or decreased disease," "absent," or "progression."

6.10.2 Modified World Health Organization criteria for response

The mWHO criteria were developed as a hybrid tumor response classification system using elements of both the WHO and RECIST criteria in an attempt to more accurately measure tumor lesions and estimate tumor responses.

Definition of Index Lesion Response Using mWHO Criteria

Complete Response: Complete disappearance of all *index* lesions.

Partial Response: Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* lesions.

Stable Disease: Does not meet criteria for complete or partial response, in the absence of progressive disease. Subject with PR or CR that is not confirmed after at least 4 weeks are scored as SD unless they have new primary lesions.

Progressive Disease: At least 25% increase in the sum of the products of all *index* lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of ***any*** new lesion(s).

Definition of Non-Index Lesion Response Using mWHO

Complete Response: Complete disappearance of all *non-index* lesions.

Stable Disease: A decrease or tumor stabilization of one or more *non-index* lesions. Subject with PR or CR that is not confirmed after at least 4 weeks are scored as SD unless they have new primary lesions.

Progressive Disease: Progression of *non-index* lesion(s) (e.g., an increase in pleural effusions, or other fluid collections defined as an approximate doubling of the volume which was present at baseline or nadir, unless there is radiographic evidence of a benign cause for the fluid collection or the effusion is cytologically negative for malignant cells).

Determination of Overall Response Using mWHO

Overall Response (OR) is determined as the combination of assessments of *index* and *non-index* lesions using the following criteria:

Index Lesion Assessment	**Non-Index Lesion Assessment**	**New Lesions**	**Overall Response**
CR	CR	No	**CR**
CR	SD	No	**PR**
PR	CR or SD	No	**PR**
SD	CR or SD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	**Any**	**Yes**	**PD**

Best OR is the best confirmed response designation over the study as a whole, recorded between the date of first dose until the last tumor assessment for the individual patient in the study. The assessment of response at 12 weeks has particular emphasis due to the mechanism of action of ipilimumab inducing immune responses as basis for clinical responses. For the assessment of best OR, all available assessments per patient are considered. CR or PR determinations included in the best OR 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.

Patients will be assessed for efficacy by CT of chest, abdomen, and pelvis at baseline and every 6 weeks while on study and every 3 months thereafter, regardless of the location of known metastases. Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at screening and during subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination.

MRI of the brain will be used if brain metastases are being treated on study or if neurologic symptoms suggest concern for new or progressive disease within the brain.

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If progressive disease is assessed based only on a new lesion(s) found on bone scans, additional imaging studies of the lesion(s) should be performed to confirm the malignant nature of the new findings on the bone scan. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless

the lesions seen on the correlative imaging studies performed of this area meet the criteria for progression. New areas of abnormal uptake on a bone scan represent progressive disease.

6.10.3 Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the 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.

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 Total 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.

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).

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.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria: 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).

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): 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	$\geq$ -50%	irPR
				<-50% to <+25%	irSD

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**
Stable Disease	Any	Any	Any	>+25%	irPD
				<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

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.

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 modified WHO criteria.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Overall, this study will require 32 evaluable patients. We estimate that we will accrue 1-2 patients per month; therefore, thus, the minimum study duration will be 16 months (2 accruals per month) and the maximum is 32 months (1 accrual per month for 32 patients).

Current literature and experience with ipilimumab in metastatic melanoma in this patient population shows that we can expect ipilimumab + SABR will not be considered promising in this patient population if at most 15% of patients are progression-free and alive at 6 months, because that is the expected 6 month PFS for ipilimumab alone[1]. For this agent to be considered promising in this patient population, we would expect an improvement in the 6-month PFS rate to at least 35% with this regimen in this patient population. Constraining the Type I and II error rates to 10% each, the study design will require 32 evaluable patients to test these hypotheses regarding the 6-month PFS rate with ipilimumab when given in combination with the stereotactic ablative radiation therapy in this patient population. If we see at least 8 patients who have are alive and progression-free at 6 months after initiation of treatment out of the 32 evaluable patients, we will consider this sufficient evidence that this regimen has promising activity in this patient population. Otherwise, if 7 or fewer patients have are alive and progression-free at 6 months, we will consider this regimen to not be sufficiently active in this population of oligometastatic melanoma patients.

7.2 Statistical methods

All evaluable patients will be included in calculating the 6-month PFS rate for the study along with corresponding 95% binomial confidence intervals (assuming the number of patients who are progression-free and alive at 6 months is binomially distributed). The numerator will be the number of patients at 6-months from enrollment who have either a complete response, a partial response, or stable disease (i.e. have not progressed) on re-staging imaging and who are alive. The denominator will be the number of patients on trial who received ipilimumab and SABR.

In addition, several secondary endpoints will be evaluated in these subjects:

- ***Toxicity and Tolerability***. Frequency and severity of adverse events and tolerability of the regimen in each of the patient groups will be collected and summarized by descriptive statistics. As per NCI CTCAE v4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that

is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described. We will also assess tolerability of the regimens through assessing the number of patients who required dose modifications and/or dose delays. In addition, we will also capture the proportion of patients who go off treatment due to adverse reactions or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. These tolerability measures will be assessed within each of the treatment arms and we will explore differences in these measures between the arms. All patients who have received at least one dose of any of the therapeutic agents in a treatment arm will be evaluable for toxicity and tolerability.

- ***Overall response***. All evaluable patients (i.e. eligible patients who have received at least two doses of ipilimumab and SABR) will be assessed in terms of their best response to therapy by both mWHO and irRC. Those who achieve a partial response (PR) or complete response (CR) will be considered responses and the overall response rate will be calculated as the number of PRs and CRs divided by the total number of evaluable patients. Best overall response rate will be reported taking into account all post-treatment imaging.
- ***Overall survival and progression-free survival as continuous time-to-event outcomes***. All evaluable patients will be used for this analysis. Kaplan-Meier curves will be used to estimate overall and progression-free survival. Each of these variables is measured from the date of study registration to the date of event (i.e., death or disease progression). In the case of the overall survival endpoint the date of last follow-up is to be used if no event has occurred at their last evaluation. In the case of the progression-free survival endpoint the date of last tumor assessment is to be used if no event has occurred at their last evaluation.
- ***Correlative markers***: Several correlative markers will be explored in this trial in relation to clinical outcomes of interest, and in particular in relation to the primary endpoint of 6-month PFS rate. Given the limited overall sample size as well as the relatively limited expected proportion of patients who are progression-free and alive at 6 months, these analyses will be largely exploratory and hypothesis-generating in nature. Markers will be summarized univariately in a quantitative manner and also summarized by clinical outcome group (e.g. prog-free and alive at 6 months vs. not). Graphical analyses will be largely used to assess potential patterns and relationships; e.g. side-by-side boxplots to assess differences in continuous marker levels between those with vs. without the clinical improvement. We may also explore changes in these markers in relation to baseline, with clinical outcome incorporated through use of different plotting characters. Overall, hypothesis testing will largely be avoided given the sample size limitations but we will still obtain important preliminary data that can inform future studies and help better understand the mechanisms of this treatment regimen in this patient population.

Statistical and Data Analysis:

Assistance in statistical analysis will be provided by the Center for Biostatistics for The Ohio State University Comprehensive Cancer Center.

7.3 Subject Population(s) for Analysis

All subjects enrolled in the study received at least two doses of ipilimumab and SABR will be used for analysis of the primary endpoint.

7.4 Interim Analysis- Safety

Prior use of 3mg/kg ipilimumab alone has resulted in a 10-15% grade 3+ autoimmune related toxicity rate. If the addition of SABR to ipilimumab doubles the risk of grade 3+ autoimmune related toxicity, that would be unacceptable. Therefore, our null hypothesis will be that 70% or more of the patients will be severe immune related toxicity-free. We will conduct an interim analysis after the treatment of 18 patients to assess the null hypothesis versus the alternative hypothesis of 90% or more of the patients will be severe immune related toxicity-free. If at the interim analysis 14 or more patients are severe immune related toxicity-free then we will continue to enroll to the planned enrollment of 32 patients. If 5 or more patients have severe immune related toxicities we will consider this combination too toxic for further investigation.

8.0 STUDY CALENDAR

See appendix II.

9.0 INVESTIGATIONAL PRODUCT: IPILIMUMAB

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study, whether blinded or unblinded. In this study, the investigational product is ipilimumab and is unblinded.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, noninvestigational product(s) is/are: SABR.

The investigational combination is the use of ipilimumab with SABR. Individually ipilimumab is approved for use in metastatic melanoma and SABR is a commonly used palliative treatment for oligometastatic or oligoprogressive cancers of many types.

9.1 Identification

Ipilimumab is available in concentrations of 5 mg/mL (50 mg/10 mL and 200 mg/40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

9.2 Packaging and Labeling

BMS will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement.

9.3 Storage, Handling, and Dispensing

9.3.1 Storage

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature ≥ 2°C and ≤ 8°C.

9.3.2 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.

9.3.3 Dispensing

It is the responsibility of the investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

9.4 Drug Ordering and Accountability

9.4.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from BMS. Investigators must complete a Drug Request Form and email it to: distribution.allentown@thermofisher.com.

If for any reason the e-mail drug request form is not successfully transmitted, contact Emily Kahora at Fisher Clinical Services:

Phone: +1 484.538.2121
Fax: +1 610.871.9382
Email: emily.kahora@thermofisher.com or www.fisherclinicalservices.com.

It is recommended you send a test message to the Fisher Clinical Service e-mail address upon receipt of the Drug Request Form. Please include in the subject line: "BMS IST Drug Order -- Test." This will ensure your site is recognized by Fisher and your future orders will be received without incident.

Ipilimumab vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from Fisher Clinical Services on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs.

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. **It is imperative that only product designated for this protocol number be used for this study.** To help segregate product for this study from other investigational or marketed product, stickers bearing the BMS protocol number will be provided and should be affixed to the front of the outer carton just above the company name so as not to obscure any marking.

9.4.2 Re-Supply

Reorders should be emailed directly to Fisher Clinical Services (distribution.allentown@thermofisher.com) for shipment within 5 business days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 5 business days from BMS receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

9.5 Ipilimumab Accountability

It is the responsibility of the investigator to ensure that a current record of ipilimumab disposition is maintained at each study site where ipilimumab is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.

- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

9.6 Ipilimumab Destruction

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.

10 ADVERSE EVENT REPORTING

10.1 Collection of Safety Information

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational combination, whether or not considered related to the investigational combination.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

10.1.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.4 for reporting pregnancies.)

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

10.1.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

10.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression “reasonable causal relationship” is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

10.3 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.

The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

10.3.1 Serious Adverse Events

Following the subject’s written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

AND reported to the Ohio State University IRB via the electronic Buck-IRB website reporting system: http://orrp.osu.edu/irb/buck-irb/ per OSU IRB policy.

Ohio State University Cancer IRB
Office of Responsible Research Practices
1960 Kenny Road
Columbus, Ohio 43210
Phone: 614 292-5958

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

10.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of

efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

10.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing nonserious AE worsens in its intensity, or if its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described in the medical record.

10.3.4 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information

- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 3 days before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to BMS, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

10.3.5 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

All SAEs must be sent to BMS as stated above (Section 10.3.1, paragraph 1).

10.4 Data and Safety Monitoring Committee

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with BMS, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

11.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

11.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All sections of each CRF must be completed and each page identified with the patient's assigned registration number and initials. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in ink. Only the Principal Investigator or authorised Co-investigator can sign the CRFs for assurance of exactitude and completeness of each page.

If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For

clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

11.5 Monitoring and Audit

This study will be monitored by Ohio State University Comprehensive Cancer Center per their institutional guidelines.

In addition, an agent of BMS, the FDA or another national regulatory authority may audit the study centre in depth for study quality assurance. This audit may include review of all source documents, treatment records, original clinic case notes, etc.

Patient confidentiality will be maintained at all times and consent for this review will be obtained before entry of the patient into the study by the patient's signature on the consent form.

11.6 Records Retention

The investigator must arrange for the retention of the patient identification codes (i.e. hospital/unit code, trial identification code and trial number) for as long as the BMS requests after completion or discontinuation of the clinical trial. Other source documents, such as patient files and clinic case notes, must be retained for the maximum period of time permitted by the hospital, institution or private practice, and if this is less than BMS requires after the completion or discontinuation of the clinical trial, then BMS must be notified to arrange record retention.

The investigator will also be required to retain his/her copies of the CRFs and other study documentation for as long as BMS requests this. If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintaining the study documentation, BMS must be notified (in writing) so that adequate provision can be made with regard to the patient identification codes, their copies of the study documentation (e.g. copies of the CRFs) and other source data (if available). This responsibility may be transferred to Glaxo SmithKline who will make arrangements to store the data..

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

12.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures

In addition, the investigator must provide the following documentation:

- The IRB annual re-approval of the protocol.
- The IRB approval of any revisions to the informed consent document or amendments to the protocol.

Details of the IRB's composition including names of their members, their qualifications and what function they perform on the committee (e.g.: chairman, specialist, lay-member) will be made available to conform to regulations governing the conduct of clinical trials. If available, the constitution of the IRB must also be supplied.

13.0 TISSUE/SPECIMEN COLLECTION AND CORRELATIVE ANALYSIS

13.1 Background

The purpose of this correlative study is to evaluate if highly conformal, high dose per fraction radiation therapy like SABR, given concurrently with ipilimumab will improve

progression-free survival for patients with oligometastatic melanoma (3 or fewer sites of metastatic disease).

13.2 Screening for Eligibility

All patients enrolled on the study will be eligible for the correlative studies.

13.3 Planned Correlative Analyses

Blood and tissue samples will be collected for research purposes. Planned studies include exploration of certain gene mutations and serum markers as predictors of response to ipilimumab and SABR combination treatment. Proteomics expression patterns will be used to determine if they are a prognostic or predictive marker for treatment response. We plan to also evaluate if primary tumor cells and melanoma stem-like cells can be isolated from the tissues using stem-like cell isolation techniques. These cells may be transitioned to long-term cell lines for further research.

There are currently no standard prognostic or predictive markers to evaluate or anticipate outcome of ipilimumab and SABR combination therapy. This study provides the opportunity for exploratory analysis of several hypotheses that may predict outcome. Hence, we propose to collect pilot data comparing pre-treatment with post-treatment proteomic and genetic features in this cohort of melanoma patients. Furthermore, we will conduct investigations of genomic and proteomic levels to more completely understand melanoma biology and further elucidate its response in the setting of current ipilimumab and high dose per fraction radiation therapy.

Immune tolerance and immunoediting are the two principle mechanisms by which solid tumors evade detection and destruction by the immune system. Immune tolerance is a process by which tumor cells become resistant to activated immune effector cells. In contrast, immunoediting occurs when tumors manipulate their microenvironment by creating complex local and regional immunosuppressive networks that consist of various tumor-derived cytokines and other soluble factors. Consequently, we will include relevant cytokine and protein biomarkers that modulate immunoediting and immunosuppression.

13.4 Specimen Collection

Optional blood and serum samples for correlative analysis will be collected pre-treatment (Week 1), prior to 2nd ipilimumab infusion (Week 4), before initiation of SABR (week 5), prior to 3rd ipilimumab infusion (Week 7), prior to 4th ipilimumab infusion (Week 10), 2 weeks after ipilimumab (Week 12), and at weeks 16, 20, 24, 35, and 50. (Please see section 3.4 Figure).

Whole blood will be collected at each time point for whole blood marker and serum marker assessments. For whole blood markers, 30 mL blood will be collected in 3 x 10-mL heparin containing tubes. For serum markers, 10 mL blood will be collected in a 10

mL red top tube.

Tissue sections: Genomic DNA from the tissue sections of patients biopsy or resection material will be isolated and paired with matched blood samples and will be used for the following analysis:

1. We propose to sequence them to identify the key gene mutational status and whether the mutation is germline or somatic.
2. Determination of the wild type v mutant type ratio of key melanoma genes such as BRAF, NRAS, KIT, CDKN2A, PIK3CA, PTEN, TP53, MEK, EGFR, Akt, etc. using castPCR technique.
3. The tissue microarray (TMAs) obtained after Dermatopathologist selected/ reviewed area will be used for fluorescence based Immunohistochemistry and the expression intensity of images will be scored using an automated system.
4. The co-localization and subcellular localization and intensity of histologic staining will also be determined.
5. Tumor antigens such as Melan-A, NY-ESO-1, MAGE, MART-1, gp-100, tyrosinase, PSA, PAP, and PSMA.

Additional post-treatment biopsy or resection tissues will also be analyzed if they become available. Planned post-treatment biopsy is not part of this study.

Blood and Serum Markers: We propose to determine the expression levels of various seromic proteins and cell surface markers. The marker proposed includes:

1. Absolute lymphocyte count (ALC), CD152 (CTLA-4) by flow cytometry, CD28 by flow cytometry, LDH.
2. T cell activation markers CD3, CD4, CD8, HLA-DR, ICOS, C11b, CD69, CD137, CD154, CXCL16, CTLA-4, and PD-1.
3. T cell suppressor – Myeloid derived suppressor cells CD14 and HLA-DR.
4. T helper 17 (Th17) cells and related cytokines IL-17 and IL-22.
5. Regulatory T cells ‘Tregs’ CD4, CD25/LAP and FoxP3, CD127, IDO.
6. Ratio of effector and regulatory T cells “Teff/Treg”.

7. B-7 family costimulatory molecules: CD80(B7-1), CD86(B7-2).
8. Bioplex Assays using serum samples: Human 8-plex assay; IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, TNF-α, CXCL9 and Human Th17 cytokine panel; IL-1β, IL-4, IL-6, IL-10, IL-17A , IL-17F , IL-21 , IL-22 , IL-23 , IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α, IL-17A/F.

Blood specimens will be picked up by personnel from the laboratory of Dr. Palanichamy for subsequent processing and analysis.

Kamalakannan Palanichamy, Ph.D.
Department of Radiation Oncology
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute
400 W. 12th Avenue, Ste 385E
Columbus, OH 43210
Office (614)-685-4245
Fax (614) 293-4044
Email: Kamalakannan.palanichamy@osumc.edu

13.5 Correlative Strategy

1. Serum and blood sample volume: From patient to patient relative abundance of proposed markers may vary widely due their immune response and individual variability. Hence there may be some markers which would require higher volume of samples because of their low abundance / antigen presentation which would be a bottle neck for the proposed analysis. *We propose to overcome the sample volume limitations by two approaches i) by multiplexing the assays and ii) by positive selection of that particular antigen using antibody coated bead technology.*

2. Fluorescence based IHC: Historically conventional IHC was used for scoring by dermatopathologists and introducing this new approach to predict the outcome may not be a head to head comparison. *We propose to stain TMA both by conventional IHC and Fluorescence based IHC. A Dermatopathlogist will score the*

conventional TMAs and the scores will be compared to the scores generated by automated system to avoid discrepancy.

The expected outcome of this study is to identify the endpoints that correlate with, or predict the following events;

1. Clinical benefit
2. Progression-free survival
3. Overall Survival
4. Immune related adverse events
5. Antitumor immune response in real-time
6. Characterizing the steps involved in abscopal effect with radiotherapy
7. Identifying the subset which will derive more clinical benefit from the genetic and proteomic profiles.
8. Developing biomarkers to predict the response to treatment, PFS, and OS at early stage of treatment and also duration of response.

13.6 Confidentiality/Storage

- The patient's name and/or other identifying information should be removed from the pathology report, blocks, or slides. However, the surgical pathology numbers and de-identified information must NOT be removed.
- De-identified samples will be stored securely for an indefinite period of time in the laboratory of Dr. Palanichamy

14.0 STUDY FINANCES

14.1 Funding Source

The study is funded through a grant from BMS.

14.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by OSUMC prior to participation in this study.

14.3 Subject Stipends or Payments

There is no subject stipend/payment.

15.0 PUBLICATION PLAN

Any formal presentation or publication of data from this trial may be published after review and comment by BMS (Grantor) prior to any outside submission. BMS must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge BMS's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of BMS and, in accord with the trial contract and shall not permit disclosure of BMS confidential or proprietary information.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the Grantor for the purposes of performing the study, will be published or passed on to any third party without the consent of the Grantor.

16.0 REFERENCES

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Appendix I: ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.
5	Dead

Appendix II: Study Schedule

	Pre-Treatment		During Treatment						Follow-Up visits start within 30 days of last dose (+/- 20 days), with the goal of 30 days for the first follow-up visit.			
	≤ 4 Week prior to first treatment	≤3 days Prior To first treatment	Day 1	Prior to Week 4	Week 5 Before SABR	Prior to Week 7	Prior to Week 10	Week 14	Q3 months for first 2 years	Q6 months for year 2- 5	Annu -ally for 5 years	At Progression
History and physical exam	X			X				X	X	X	X	
Consent Obtained	X											
Record Prev. Therapies	X											
Blood Specimen Banking			X	X	X	X	X	^	$			
Vital signs	X		X	X		X	X	X	X	X	X	
EKG	X											
Diagnostic biopsy	*											*
Contrast-enhanced CT or MRI of the abdomen and pelvis	X					X@		X@	*	*	*	
CT chest	X					X		X	*	*	*	
Whole-body PET-CT scan of body (optional)	X								*	*	*	
CBC w/diff & ANC, platelets	X		X	X		X	X	X	X	X	X	
CMP including LFTs	X		X	X		X	X	X	X	X	X	
Thyroid Fxn and ACTH level	X			X		X	X	X	X	X	X	
CrCl assessment	X											
Urinalysis	X											
Continue to next page												

	≤ 4 weeks prior to first treatment	≤3 days Prior To first treatment	Day 1	Prior to Week 4		Prior to Week 7	Prior to Week 10	Week 14	Q3 months for first 2 years	Q6 months for year 2- 5	Annu al-ly for 5 years	At Progression
Serum pregnancy test	X	X[x]										
HIV, Hep B and C test	X											
Ipilimumab			X	X		X	X					
SABR						X						
Adverse event evaluation			X	X		X	X	X	At 90[xx] days post-treatment			
Tumor banking	*											*

*preferred/at the discretion of the treating physicians

[x]mandatory

^ Post-treatment blood draw will occur at week 12 (two weeks after 4th ipilimumab infusion)

$ During the follow-up period blood collections will occur at week 16, week 20, week 24, week 35 and week 50 per Section 3.4.

@ Will delayed if ipilimumab dosing is delayed: CT will be prior to infusion 3, and 4 weeks after infusion 4.

[xx] SAEs are to be reported to sponsor and IRB up to 70 days after last treatment with ipilimumab per protocol

Appendix III: Comparison between WHO criteria and the irRC[2]

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart