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NCT Number:	NCT03999749
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CLINICAL STUDY PROTOCOL

A Phase II Study of the Interleukin-6 Receptor Inhibitor Tocilizumab in Combination with Ipilimumab and Nivolumab in Patients with Unresectable Stage III or Stage IV Melanoma.

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NYULHStudy Number:	*S19-00008; BMS CA209-76Y; Genentech ML41555*
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Study Product:	*Tocilizumab*
Study Product Provider:	*Bristol-Myers Squibb Company* *Genentech*
Coordinating Center:	*NYU Langone Health* *Perlmutter Cancer Center* *Clinical Trials Office* *PCC-QAU@nyulangone.org*
Participating Sites	*NYU Langone Health, New York NY* *Dana Farber Cancer Center, Boston MA* *The Angeles Clinic and Research Institite, Los Angeles CA* *Massachusetts General Hospital*
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STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase II Study of the Interleukin-6 Blocking Antibody Tocilizumab in Combination with Ipilimumab and Nivolumab in Patients with Unresectable Stage III or Stage IV Melanoma

Protocol Number: S19-00008; [BMS CA209-76Y; Genetech ML41555]

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), cGCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining previous approval of BMS. and of the IRB. I will submit the protocol amendments and/or any ICF modifications to BMS. And the NYU IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.

Information developed in this clinical study may be disclosed by BMS to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AJCC	American Joint Committee on Cancer
alloMLC	allogeneic mixed lymphocyte culture
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	as-treated population
AUC	area under the concentration-time curve
BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase. A human gene that makes a protein called B-Raf.
CD	clusters of differentiation
CI	confidence interval
cGCP	current Good Clinical Practice
CNS	central nervous system
CR	complete response
CRF	case report form, paper or electronic
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated antigen-4
CTO	Clinical Trials Office
DC	Dendritic cell
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
EOMES	eomesodermin gene
FDA	Food and Drug Administration
FOXP	forkhead box P gene
FSH	follicle stimulating hormone
FU	follow-up
GLP	Good Laboratory Practices
hERG	human ether-a-Go-go related gene

HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICOS	inducible T-cell co-stimulator gene
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse events
IMP	investigational medicinal product
I-O	immuno-oncology
IP	Investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
irBOR	immune-related best overall response
irCR	immune-related complete response
irPD	immune-related progressive disease
irPFS	immune-related progression-free survival
irPR	immune-related partial response
irRC	immune-related response criteria
irRR	immune-related response rate
irSD	immune-related stable disease
irSPD	immune related sum of products of diameters
irUN	immune-related unknown response
IV	intravenous(ly)
LD	longest diameter
LFT	liver function test
MDSC	Myeloid derived suppressor cell
MHC	major histocompatibility complex
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
N	number of patients or observations
N/A	not applicable
NCI	National Cancer Institute

NOAEL	no observed adverse effect level
NOEL	no observed effect level
NK	natural killer
NSCLC	non-small cell lung cancer
NYU	New York University
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCC	Perlmutter Cancer Center
PD	progressive disease
PD-1	programmed cell death protein
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
pT	Probability of toxicity
QD	once daily
ORR	objective response rate
qRT-PCR	quantitative real-time polymerase chain reaction
QTc	corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SFU	survivor follow-up
SPD	summary of products of diameters
SRC	Safety Review Committee
Th1	Type 1 T helper cells
TIL	tumor infiltrating lymphocytes
TNF	tumor necrosis factor
TPI	toxicity probability interval
Tregs	regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	Unites States
WBC	white blood cell

WHO	World Health Organization
WOCBP	women of childbearing potential
WT	wild-type

SYNOPSIS

Protocol Number	S19-00008
Title:	A Phase II Study of the Interleukin-6 Receptor Inhibitor Tocilizumab in Combination with Ipilimumab and Nivolumab in Patients with Unresectable Stage III or Stage IV Melanoma
Investigational Product:	Tocilizumab
Study Center:	Four study centers in the United States: NYU-Langone Health. New York City, Dana Farber Cancer Center and Massachussetts General Hospital in Boston and The Angeles Clinic, Los Angeles
Phase:	II
Indication:	Unresectable Stage III or Stage IV Melanoma
Objectives:	**Primary Objectives:** • Determine the safety, tolerability, and rate of grades 3-5 immune-related adverse events up to 6 months from therapy initiation when tocilizumab is administered every 6 weeks for 5 doses from day 1, cycle 1 in combination with a regimen of ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a 12-week induction period, then administered with nivolumab at 240 mg flat dose every 2 weeks up to week 24, and nivolumab alone in maintenance after week 24 at 480 mg every 4 weeks for up to 2 years in patients with unresectable Stage III/Stage IV melanoma. • Determine the preliminary antitumor activity defined by overall response rate (CR + PR at week 24) of tocilizumab administered in combination with ipilimumab and nivolumab to patients with unresectable Stage III or Stage IV melanoma.
	Secondary Objective • Determine the progression-free survival of tocilizumab administered in combination with ipilimumab and nivolumab to patients with unresectable Stage III or Stage IV melanoma. • Determine the overall survival of tocilizumab administered in combination with ipilimumab and nivolumab to patients with unresectable Stage III or Stage IV melanoma.
	Exploratory Objectives: • Determine the pharmacodynamic effect of the 3-drug combination (tocilizumab, ipilimumab, nivolumab) dose regimen on biomarkers in peripheral blood samples and tumor biopsy specimens.
Study Design:	This is a Phase II, open-label, single arm study. The study will consist of an assessment of the safety and tolerability of tocilizumab administered concurrently at 4 mg/kg every 6 weeks for 5 doses in combination with ipilimumab and nivolumab for four induction doses to week 12, then

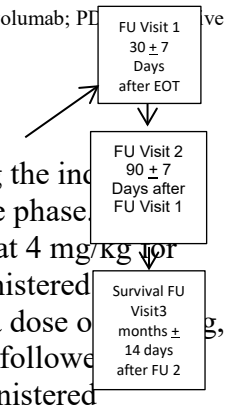
maintenance nivolumab alone up to two years to patients with advanced melanoma. Treatment will be divided into induction and maintenance phases.

It is anticipated that this clinical study will inform the use of this 3-drug combination for further phase II and/or phase III clinical testing. The trial will include an assessment of the pharmacodynamic activity of tocilizumab administered in combination with ipilimumab and nivolumab. A study schematic is presented below:

Figure 1: Study Schematic

Figure 1: Study Schematic

Abbreviations: C = cycle, D= day; FU = follow-up; Ipi = ipilimumab; Nivo = nivolumab; PD ve disease;.



Each treatment cycle will be 42 days (6 weeks) during the ind phase, and 84 days (12 weeks) during the maintenance phase. Tocilizumab will be administered (IV) every 42 days at 4 mg/kg for each 42-day induction treatment cycle. On days administered combination, nivolumab will be administered first at a dose o g, followed by ipilimumab at 1 mg/kg, and immediately followe tocilizumab. Nivolumab and ipilimumab will be administered intravenously (IV) each over 30 minutes, with a 30-minute rest period between infusions on Days 1 and 22 of each 42-day induction treatment cycle. The induction phase will last for 2 treatment cycles. During the maintenance phase, tocilizumab will be administered IV every 42 days during the first 84-day maintenance treatment cycle only up to week 24. Nivolumab will continue to be administered at 240 mg flat dose every 2 weeks (i.e., at Days 1, 15, 29, 43, 57, and 71 of each 84-day treatment cycle up week 24, then after week 24 at a dose of 480 mg every 4 weeks for up to two years). On days administered in combination, nivolumab will be administered first, followed by tocilizumab. Patients will continue maintenance treatment with their tocilizumab and nivolumab dose regimen for up to week 24, then nivolumab alone to 2 years or until progression of disease, discontinuation due to toxicity, withdrawal of consent, or any other reason as specified per protocol.

A total of 67 patients in this trial will allow a sufficient number of patients to provide a preliminary assessment of rates of grades 3-5 irAEs and overall response rates (ORR) as co-primary endpoints.co-primary endpoints.

Enrollment will proceed with administration of tocilizumab in combination with ipilimumab and nivolumab as described in Table 1:

Table 1. Regimen for Tocilizumab with Ipilimumab and Nivolumab During Induction

Dose Cohort	Tocilizumab Dose	Ipilimumab Dose	Nivolumab Dose
2	6 mg/kg IV	1 mg/kg IV	3 mg/kg IV
1	4 mg/kg IV	1 mg/kg IV	3 mg/kg IV
-1	2 mg/kg IV	1 mg/kg IV	3 mg/kg IV

If Cohort 1 shows unacceptable toxicity in the first 12 patients, defined as a 50% rate of drug related DLTs, then Cohort -1 will be tested as indicated in this study. Decisions regarding dose de-escalation will be guided by the incidence of drug-related DLTs occurring within 42 days (6 weeks; through Day 42 of induction cycle 1) of initiation of study therapy. This observation interval is based upon inclusion of the known median times to onset of common immune-related adverse events (irAEs) attributed to ipilimumab and nivolumab and allows for a substantial amount of time for unexpected toxicities with the combined administration of tocilizumab with ipilimumab and nivolumab to emerge. Patients who do not complete the 42 day DLT-observation period for reasons other than an adverse event will be replaced. As described below, if at the conclusion of stage I both the efficacy and toxicity endpoints have not been met, i.e., we have seen neither a reduction in the toxicity (irAE of grades 3-5 $\geq$6/18) nor an increase in efficacy (responses$\leq$10/18), then we will stop early and consult with IRB and/or FDA.

Safety Review:

All available clinical and laboratory data, and the nature, time of onset, and time to resolution of any DLTs observed will be reviewed to determine whether an alternate dose schedule should be examined after consultation between the Investigators, the FDA and BMS, if needed. If agreed upon, the alternate schedule will be identified by a protocol amendment.

The data will be reviewed by the NYU-Perlmutter DSMC which will also review all safety data, specifically to review all Grade 3 or greater irAEs, or grade 2 irAEs that do not resolve to grade 1 or less with therapy.

Definition of Dose-Limiting Toxicity

For the purpose of guiding dose escalation decision making, hematologic and non-hematologic DLTs will be defined separately and will be determined based on the incidence, severity, and duration of study drug-related AEs occurring within 42 days (6 weeks; through Day 42 of induction cycle 1) of initiation of study therapy. The dose escalation decision for Tocilizumab will be determined by an assessment of whether the addition of tocilizumab has potentially increased the toxicity associated with ipilimumab and nivolumab or potentially decreased the response rate of the regimen.

	The following AEs, if assessed to be related to tocilizumab, will be considered DLTs: Hematologic toxicity: • Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) lasting > 7 days. If neutropenia is attributed to tocilizumab, ANC is to be repeated on Day 6 to determine if it is a DLT • Febrile neutropenia (ANC < 1,000/μL with a single temperature > 38.3°C [101.0°F] or 38.0°C [100.4°F] for > 1 hour) • Grade 4 thrombocytopenia (platelet count < 25,000/μL) • Grade 3 thrombocytopenia (platelet count 25,000/μL to 50,000/μL) with clinically important bleeding. Non-hematologic toxicity: The etiology of all other Grade 3 or Grade 4 nonhematologic toxicities will be indistinguishable from immune related toxicities. Immune-related toxicity: All Grade 3 or Grade 4 immune-related toxicities will be considered as potential DLTs. Immune-related toxicities among patients treated with nivolumab and ipilimumab have clustered among skin, gastrointestinal, endocrine, and liver-related events as follows: • Skin: alopecia, dry skin, hyperhidrosis, night sweats, pruritus, rash/desquamation, toxic epidermal necrolysis, urticaria, vitiligo. • Gastrointestinal: abdominal discomfort or pain, anal ulcer, colitis (including ulcerative, hemorrhagic, ischemic, and megacolon), constipation, cramping, diarrhea (including hemorrhagic), diverticulitis/diverticulum, duodenitis, dyspepsia, dysphagia, enteritis, esophagitis, gastritis (including erosive), gastrointestinal hemorrhage (including rectal), hematochezia, ileitis, ileus, intestinal obstruction, intestinal perforation (including small and large intestines), melena, nausea, pancreatitis, peritonitis, stomatitis (including aphthous), vomiting, vasculitis gastrointestinal. • Endocrine: adrenal insufficiency (including Addison disease), glucose tolerance impaired, hyperthyroidism hypogonadism, hypophysitis/hypopituitarism (autoimmune), hypothyroidism, pituitary enlargement, thyroiditis (autoimmune). • Liver: hepatitis, jaundice.

	Other treatment-related asymptomatic Grade 3 and Grade 4 laboratory investigations, excluding cardiac function tests, may be evaluated by the SRC to determine whether dose cohorts should be expanded.
Number of Patients:	Up to 67 patients are expected to be treated for the evaluation of immune related toxicity at the selected dose. If the first dose level is modified based on the first 12 patient evaluation, then a max of 79 patients would be treated in total.
Treatment:	Tocilizumab is supplied for intravenous injection: as 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution. Nivolumab is available as sterile dose formulations of 10 mg/mL and will be supplied to sites in 100mg/10mL vials to be administered IV as an infusion over 30 minutes. Ipilimumab is available as a sterile dose formulation at 5 mg/mL and will be administered IV as an infusion over 30 minutes. Nivolumab and ipilimumab are not to be administered as an IV push or bolus injection. On days administered in combination, nivolumab will be administered first at a dose of 3 mg/kg, followed by ipilimumab at 1 mg/kg with a 30-minute rest period between infusions immediately followed by tocilizumab at 4 mg/kg.
Study Duration:	The total duration of the study from the first dose of study drug to final analysis of toxicity and tolerability is expected to be 36 months. Survival will be assessed for 3 years beyond a maximum of 2 years of treatment, i.e., a total of up to 5 years. Patients may discontinue from treatment because of disease progression, unacceptable toxicity, withdrawal of consent, or at the discretion of the Investigator. The last visit for each patient will be defined as the follow-up visit which is no less than 90 days after the patient's end-of-treatment visit. The last visit is either 90 days after the last dose or whenever a study drug-related toxicity has resolved, stabilized, or been deemed reversible, whichever is latest. The end of the trial will occur on the last visit of the last patient.
Study Population:	**Inclusion Criteria:** 1. Patients must have signed and dated an Institutional Review Board/Independent Ethics Committee -approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care 2. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study. 3. All patients must be either Stage IIIb/c/d or Stage IV according to the American Joint Committee on Cancer (AJCC) (8th edition) and have histologically-confirmed melanoma that is felt to be surgically unresectable in order to be eligible. Please refer to the AJCC Cancer Staging Manual, 8th edition for a description of tumor, lymph node, metastasis and staging.

	• All melanomas, except ocular/uveal melanoma, regardless of primary site of disease will be allowed; mucosal melanomas are eligible. • Patients must not have received prior anticancer treatment for metastatic disease (for example, but not limited to, systemic, local, radiation, radiopharmaceutical). o Exceptions: Surgery for melanoma and/or post-resection brain radiotherapy (RT) if central nervous system (CNS) metastases and local radiation for locoregional disease and/or prior treatment with adjuvant nivolumab, dabrafenib and trametinib, pembrolizumab, interferon (IFN) or ipilimumab (IPI) (as described in Exclusion Criterion 8). • All patients must have their disease status documented by a complete physical examination and imaging studies within 4 weeks prior to the first dose of study drug. Imaging studies must include computerized tomography (CT) scan of chest, abdomen, pelvis, and all known sites of resected disease in the setting of Stage IIIb/c/d or Stage IV disease, and brain magnetic resonance imaging ([MRI]; brain CT is allowable if MRI is contraindicated). • The complete set of baseline radiographic images must be available before treatment initiation. **Exclusion Criteria:** 1. Patients with carcinomatosis meningitis or current ocular/uveal melanoma are excluded. 2. Patients with previous non-melanoma malignancies are excluded unless a complete resection or remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include, but are not limited to, non-melanoma skin cancers, in situ bladder cancer, in situ gastric cancer or gastrointestinal stromal tumor, in situ colon cancers, in situ cervical cancers/dysplasia, or breast carcinoma in situ). 3. Patients with active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the Principal Investigator be consulted prior to signing informed consent. 4. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
Endpoint	**Co-primary Endpoints:** • To estimate the rate of grades 3-5 irAEs with tocilizumab at 4 mg/kg for 5 doses over 24 weeks administered in combination with ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a

	12-week induction period, then administered for up to 24 weeks with nivolumab at 240 mg fixed dose every 2 weeks up to week 24, then after week 24 at 480 mg flat dose every 4 weeks thereafter in maintenance for up to 2 years in patients with unresectable Stage III/Stage IV melanoma. Safety will be measured by physical examinations, vital sign measurements, ECOG performance status evaluations, AE assessments, laboratory testing, ECGs, oxygen saturation, and concomitant medications. • Tumor response of study treatment will be measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and irRC. RECIST 1.1 will be used for response, and irRC will only be used to decide if a patient may be treated beyond RECIST progression. **Secondary Endpoints:** Progression-free Survival RECIST 1.1 efficacy endpoints include best overall response rate, disease control rate, progression-free survival, duration of response, and duration of disease control. irRC efficacy endpoints include immune-related best overall response rate, immune-related response rate, immune-related disease control rate, immune-related progression-free survival, duration of immune-related overall response, and duration of immune-related disease control. Overall survival **Exploratory Endpoints:** • Biomarkers will be measured in peripheral blood and in tumor specimens to examine associations with clinical endpoints of response, PFS and toxicity.
Assessments	**Efficacy Assessments:** Overall response rate (CR + PR at week 24) will be determined for all subjects by RECIST 1.1 as a co-primary endpoint to evaluate efficacy along with irRC to decide if a patient with RECIST progression could continue therapy. If there is RECIST progression but the investigator feels that patients may benefit by further therapy then there must be PR or SD by irRC. Assessments of tumor status will be made during screening and at week 12 during treatment, and subsequently every 12 weeks. Tumor assessments at the end-of-treatment or 90-day follow-up visit will be performed only if not assessed within the prior 12 weeks. The individual subject's overall response rate (ORR) by 24 weeks will be assessed, and progression free survival (PFS) will also be calculated as a secondary endpoint. Other endpoints are disease control defined as outcome of complete response, partial response or stable disease by week 24. Duration of response and duration of disease control will also be calculated, as will progression-free and overall survival. **Safety Assessments**: All patients who receive any study drug therapy will be evaluated for safety and response. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, oxygen saturation, physical examinations, clinical laboratory tests, concomitant mediations, and ECOG performance status.

	Adverse events will be categorized using the most current version of Medical Dictionary for Regulatory Activities (MedDRA), and AEs and laboratory tests will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Hepatic AEs (AST, ALT, total bilirubin) will also be recorded relative to ULN. Immune-related adverse experiences among treated patients will be specifically assessed as well. **Biomarker Measures:** Pharmacodynamic effects will be assessed for measures of 1) absolute lymphocyte count; 2) serum cytokine and other analyte changes; 3) assessment of peripheral T-cell subsets, their activation status, cytokine production allogeneic mixed lymphocyte culture (alloMLC) assay changes; and 4) gene expression in peripheral blood. Pharmacodynamic effects will also be assessed for tumor-based biomarker measures of 1) infiltration of immune cells and release of immune-regulatory factors, and 2) intra-tumoral gene expression changes of immune cells.
Statistical Analysis:	**Sample Size Considerations:** The first 12 patients at the initial dose level will be evaluated for DLTs. Unacceptable toxicity will be defined by a DLT rate of ≥50%. If we observe ≥6 DLTs in these first 12 patients, we reject the null hypothesis that the DLT rate is <50% (one sided α=0.05, power=80%). If we do not reject the null hypothesis, the current dosing continues with 6 additional patients up to 18 patients (which count as the first stage of the optimal 2-stage Simon design). There will be no adjustment to the operating characteristics of the optimal 2-stage Simon design. To evaluate the co-primary endpoint of the rate of grades 3-5 treatment related immune-related adverse events, a two-stage Simon Optimal design will be used. With a total of 67 patients in two stages, (Stage 1: 12+6 patients, Stage 2: 49 patients) we can detect a reduction in the rate of the primary toxicity endpoint from 35% to 20% in grades 3-5 treatment related irAEs, with alpha of 0.05 and power of 80%. With the planned 67 patients for the co-primary toxicity evaluation of immune-related adverse events, we can simultaneously evaluate the co-primary efficacy endpoint evaluated by overall response rate (ORR) at 6 months over the 18 months of treatment. Using a Simon 2-stage optimal and minimax design, we can test the null hypothesis that the ORR rate at 24 weeks is less than or equal to 50% versus the alternative that it is 70% or greater with a maximum of 67 patients with alpha of 0.045 and power of 0.85. The evaluation of stage 1 will occur when the first 18 patients could have been observed for the 6-month period following entry. If 6 or more of the first 18 patients in stage 1 experience a grade 3-5 treatment related immune-related adverse event, the rate of toxicity would be considered unacceptable (irAE rate>=35%). If fewer than 6 patients experience a treatment related immune-related adverse event, the rate of toxicity would be considered acceptable (irAE<=20%). With an evaluation of the first 18 patients entered on study (who would complete the study before the end of study year 2) in stage 1, if we observe 10

	or fewer responses, the response rate would be considered unacceptable (ORR<=50%). Otherwise, if we observe more than 10 responses, the response rate would be considered acceptable (ORR>=70%). If both toxicity rate and response rate are acceptable - continue to complete stage 2 with up to 67 patients. If toxicity rate is acceptable, and response rate is unacceptable - increase dose to level 2 (tocilizumab 6 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients. If toxicity rate is unacceptable (due to irAE rate of grades 3-5 >=35% felt due to tocilizumab), and response rate - decrease dose level to -1(tocilizumab 2 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients. If toxicity rate is unacceptable (due to irAE rate of grades 3-5 >=35% felt due to IPI and/or NIVO), and response rate is acceptable - increase dose level to 2 (tocilizumab 6 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients. If both toxicity rate and response rate are unacceptable - stop early and consult with IRB and/or FDA. At the end of Stage 2, if there are 39 or fewer responses out of the total of 67 patients, the regimen would be considered unsuccessful. Similarly, if at the end of stage 2, there are 19 or more treatment related irAE, the trial would be considered unsuccessful to have met its objective of reducing the toxicity rate to 20% or less.

1 INTRODUCTION

Tocilizumab is a FDA approved inhibitor of the receptor for the cytokine IL-6, currently approved for the treatment of rheumatoid arthritis, giant cell arteritis and cytokine release syndrome from the use of CAR-T cells. It is also approved by the FDA for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) and systemic juvenile idiopathic arthritis (SJIA).

The purpose of this study is to evaluate the safety profile, tolerability, efficacy and immunoregulatory (pharmacodynamic) activity of tocilizumab administered in combination with ipilimumab (cytotoxic T lymphocyte associated antigen-4 [CTLA4] blocking antibody) and nivolumab (anti-programmed cell death protein-1 [PD-1] antibody) to patients with unresectable stage III or stage IV melanoma.

1.1 Nivolumab and Ipilimumab in Melanoma

Currently, the front-line and second-line standard of care treatments for unresectable Stage III/IV patients in the United States (US) include immunotherapies such as the PD-1 blocking antibodies nivolumab and pembrolizumab, the CTLA-4 blocking antibody ipilimumab, and the combination of ipilimumab combined with nivolumab. For patients whose tumors harbor a V600 mutation in the BRAF gene, vemurafenib, dabrafenib, or trametinib have been approved as single agents (Chapman, P et al 2011, Flaherty, K et al 2012), and the combination of dabrafenib with trametinib is the most commonly used regimen in that mutated population in the US and the European Union (Flaherty, K et al 2012, Ascierto, P et al 2015). The combination of ipilimumab and nivolumab at 1 mg/kg and 3 mg/kg, respectively, as induction therapy for 4 doses every 3 weeks followed by nivolumab alone as maintenance therapy at 3 mg/kg every 2 weeks results in high response rates and prolonged duration of remissions in the Checkmate-067 study (Wolchok, J et al 2013, Postow, M et al 2013, Larkin, J et al 2015).

Ipilimumab at 3 mg/kg or 10 mg/kg has shown a survival benefit in two Phase 3 randomized clinical trials in the advanced melanoma setting (Hodi et al, 2010, and Robert et al 2011), and in the U.S., it is used as a second line therapy, particularly in BRAF wild-type (WT) patients with unresectable metastatic disease. Recent data from 2018 ESMO suggested that ipilimumab and nivolumab continued to have superior progression-free and overall survival with over 4 years of follow-up in the Checkmate-067 study, with an absolute survival advantage of 7 percentage points, and an estimated median overall survival for the combination of nearly 5 years (Hodi FS et al 2018).

Nivolumab has shown a survival benefit in treatment naive patients with BRAF WT metastatic melanoma in a Phase 3, randomized clinical trial (Robert C et al 2014). In the US, it is increasingly used as a front-line regimen, as is pembrolizumab, the other US Food and Drug Administration (FDA)-approved PD-1 blocking antibody, in BRAF WT, but also in BRAF mutated patients (Robert C et al 2015).

With the recent approval of the combination of nivolumab and ipilimumab in previously untreated BRAF WT melanoma, that combination regimen may replace single agent PD-1 blocking antibodies as the treatment of choice for front line melanoma treatment in a significant proportion of patients. In the current study, we propose to build upon the combination regimen by adding a interleukin-6 receptor blocking antibody tocilizumab at

doses that are likely to be well tolerated, with a dose of nivolumab at 3 mg/kg, the approved dose as monotherapy in melanoma, and a reduced dose of ipilimumab at 1 mg/kg during the 4-dose induction regimen to reduce the potential toxicity of the combination regimen observed with the approved doses of 3 mg/kg of ipilimumab and 1 mg/kg nivolumab during the induction phase. Maintenance dosing of nivolumab when administered with Tocilizumab will be at a fixed dose of 240 mg every 2 weeks.

At the recent 2018 ESMO meeting, results were reported from the Checkmate-511 clinical trial of 1 mg/kg of ipilimumab and 3 mg/kg nivolumab during the induction phase compared with the approved doses of 3 mg/kg of ipilimumab and 1 mg/kg nivolumab during the induction phase administered for up to two years (Lebbe, C et al ESMO 2018). The curves of progression-free and overall survival were basically overlapping at a median follow up of 15 months. The incidence of grade 3-4 immune related adverse events was 48% for the standard regimen versus 33% for the "flipped dose" regimen and the rate of stopping treatment for toxicity was 33% versus 23%, suggesting that the regimen to be used in the current trial will be less toxic and just as effective as the standard dose of ipilimumab and nivolumab during induction therapy.

1.2 Interleukin-6 and Cancer

IL-6 is a glycosylated polypeptide chain having a molecular weight of nearly 25 kDa, depending on the glycosylation and the species. It has a characteristic structure made up of four long α-helices arranged in an up–up–down–down topology (Scheller J, et al 2011). It was first discovered as a B cell differentiation factor (BSF-2) which induces the maturation of B cells into antibody-producing cells (Hirano, T et al, 1985). Besides its role in immune regulation, it plays an important role in the maintenance of hepatocytes, haematopoietic progenitor cells, the skeleton, the placenta, the cardiovascular system and the endocrine as well as nervous systems. In the mouse haematopoietic system, IL-6 induces the expansion of progenitor cells by stimulating cells from the resting stage to enter the G1 phase (Kishimoto, T et al, 1995). IL-6 also supports various physiological functions by acting as a hepatocyte stimulatory factor and by inducing the acute-phase protein synthesis. It is also known to stimulate osteoclast formation, induce bone resorption and is responsible for neural differentiation (Wunderlich, F et al 2010). IL-6 supports the survival of cholinergic neurons, induces adrenocorticotropic hormone synthesis, and, in placenta, causes the secretion of chorionic gonadotropin from trophoblasts (Kishimoto, T et al 1995). IL-6 also plays a very important role in metabolism.

IL-6 binds to the IL-6 receptor (IL-6R) on the plasma membrane, and the resultant IL-6/IL-6R complex associates with gp130 and causes gp130 homodimerization to form an activated IL-6 receptor complex, which is a hexameric structure consisting of two molecules each of IL-6, IL-6R and gp130 (Taga, T et al 1996). The binding of IL-6 to IL-6R occurs at three distinct receptor-binding sites of IL-6R and gp130. However, the Ig-like domain of the human IL-6R is not involved in the direct binding of IL-6 [28]. Upon binding to the receptor and gp130, IL-6 induces various functions by activating cell signalling events (Mihara, M et al 2012). IL-6 triggers signal transduction via two forms of IL-6R: one a transmembrane 80-kDa receptor with a short cytoplasmic domain (mbIL-6R, also known as IL-6Rα, gp80 or CD126) and the other a small, extracellular, secretory soluble receptor (sIL-6R) (Hibi, M et al 1990). Classical IL-6 signaling, which

is the predominant form of IL-6 signaling, requires membrane-bound IL-6R (mbIL-6R) and is restricted to hepatocytes, some epithelial cells and certain leukocytes (Taga, T et al 1996). IL-6R contains a very short cytosolic domain that lacks the major potential motifs for transduction of intracellular cell signaling. However, gp130 (also known as IL-6Rβ or CD130) in the same hexameric complex is rich in all these potential motifs required for intracellular signaling, such as SHP-2 domain and YXXQ motif for JAK/STAT signaling. Upon binding with IL-6/IL-6R, the dimerization of gp130 leads to the activation of associated cytoplasmic tyrosine kinases, resulting in the phosphorylation of various transcription factors (Mihara, M et al 2012).

Elevated levels of IL-6 have been observed in patients with various types of cancer such as renal cell cancer (Blay, J et al 1997), melanoma (Rossi, J et al 2010), ovarian, (Luitgendorf, S et al 2008), colorectal, (Knupfer, H et al 2010) and head and neck cancer, (Tsukamoto, H et al 2017) or in patients with cachexia or wasting syndrome (Blay, J et al 1997). Elevated levels of IL-6 are inversely proportional to survival rates of cancer patients (Hoejberg L et al 2012, Dijkgraaf, E et al 2015). IL-6 signals to tumor cells through at least three major signaling pathways: JAK2/STAT3, Ras/MAPK, and PI3K/Akt cascades, which are attributed to expansion and survival of tumor cells, neo-angiogenesis, and inflammation (Ara, T et al 2013, Lesina, M et al 2011).

IL-6 exerts multiple effects not only on tumor cells, in which its action is mediated in autocrine and paracrine ways (Dijkgraaf, E et al 2015, Ara, T et al 2013, Lesina, M et al 2011) but can be secreted from myeloid cells such as macrophages (Lesina, M et al 2011), DC, and MDSC, and other tumor-associated stroma such as cancer-associated fibroblasts, endothelial, or senescent cells. IL6 is felt to be a major contributor to the dynamic cross-talk between tumor cells and activated fibroblasts in the tumor microenvironment (Karakasheva T et al 2018).

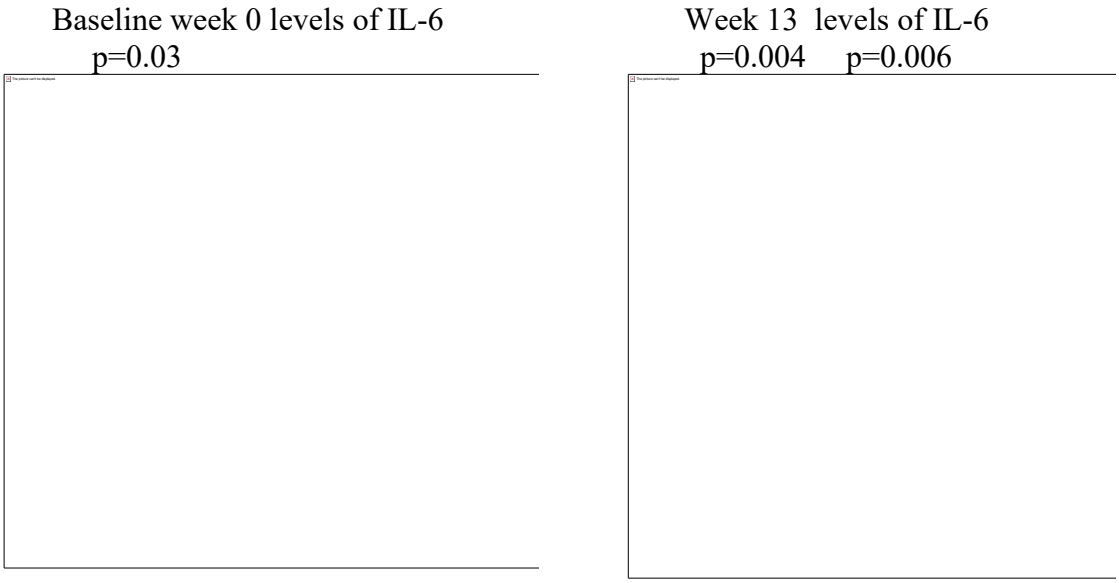
1.3 Tocilizumab in cancer patients

Tocilizumab has been used extensively in patients receiving CAR-T cells to diminish the cytokine release syndrome seen with that treatment, and is currently FDA-approved for that indication (Brudno, J et al 2012, Teachey, D et al 2016). There are no data suggesting that anti-tumor immunity is compromised by the use of tocilizumab in patients receiving CAR-T cells, and several studies have shown that CAR-T efficacy and function are unimpaired in patients treated with tocilizumab (Betts, B et al 2011). A number of anecdotal reports have suggested that tocilizumab is effective at reducing the intensity and duration of immune- related colitis in patients receiving checkpoint inhibition with PD-1 antibodies alone or in combination with ipilimumab (Rotz, S et al 2017). Tocilizumab was well tolerated in those patients, and has been used with rapid resolution of symptoms in patients that in some cases had colitis that was steroid-refractory.

1.4 CRP in Cancer

C-reactive protein (CRP), the prototypical acute phase reactant, is a pentameric protein (pentraxin) in serum whose levels rise in inflammatory states. It is synthesized by the liver, and also to a lesser degree by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes in response to interleukin-6 and interleukin-1β (DuClos,

Figure 2: Association of IL-6 levels Pre- and Post Treatment With Response



2000). CRP binds lysophosphatidylcholine on the surface of dead or dying eukaryotic cells and bacteria and activates complement via C1q. It was first identified as a molecule in the serum of patients with infection that reacted with the somatic 'C' carbohydrate antigen of pneumococcus. Normal levels in healthy individuals are up to 10 mcg/mL, but cancer patients can have very high CRP levels of greater than 500 mcg/mL.

CRP is an accepted marker for coronary disease risk, as recognized by the American Heart Association and the US Centers for Disease Control and Prevention (Yamashita, H et al 2003). A number of studies have shown that high CRP levels are associated with increased cancer risk, but the mechanisms by which that occurs is unclear, and little is known about the effects of elevated CRP on immunity in cancer patients. Recent data suggest that chronic inflammation and high CRP levels are associated with poor survival in renal cell, lung, pancreatic and breast cancer, in head and neck cancer patients treated with radiotherapy, and that CRP is associated with bony destruction in multiple myeloma (Katano AS et al 2017, Yang J et al 2017, Agnoli C et al 2017, Yasuda Y et al 2017, Hang J et al 2017, Pasterino U et al 2017, Akamine t et al 2018). There are few published data about the impact of CRP and other acute phase reactants on adaptive immunity in cancer or non-cancer states. CRP directly suppressed Th1 polarization in a murine model of experimental autoimmune encephalomyelitis (Zhang L et al 2015), and has been shown to decrease activation and maturation markers in human and murine dendritic cells by binding to CD32 (Zhang R et al 2006). A recent study showed a significant association between pre-treatment CRP levels and progression-free and overall survival in lung cancer patients treated with PD-1 immune checkpoint blockade (ICB), consistent with our published data in melanoma, which showed that acute phase reactants including CRP, serum amyloid A and P, and complement components were associated with a poor clinical outcome (Akamine T et al 2018, Weber, J et al 2018). Yet, in spite of decades of monitoring CRP and other chronic inflammatory mediators in cancer patients, little is known about the direct effects of CRP on adaptive

immunity in cancer. In the current work, we explored how CRP and other acute phase reactants impacted on the phenotype and function of T effector cells and dendritic cells from melanoma patients, and generated a hypothesis as to the mechanism by which they suppress adaptive immunity. We found that high CRP in the serum was associated with a low response rate and shorter overall survival in a recent study of the use of checkpoint inhibition in melanoma (Weber J et al 2018), consistent with the data presented herein, which support an immune suppressive role for CRP and acute phase reactants. Reduction in CRP and acute phase reactants synthesized by the liver can be achieved by the use of inhibitors of IL-1β and/or IL-6, and may result in reversal of resistance to checkpoint blockade by overcoming inhibitory effects on T cells. In the current proposal, we will employ a humanized IL-6 receptor alpha blocking antibody to decrease IL-6 levels and reduce the generation of CRP and other acute phase reactants from the liver and other cells.

Levels of CRP have long been observed to be elevated in patients with a variety of advanced cancers with levels as high as 500 mcg/mL, yet a role of CRP and other APPs in modulating the anti-tumor immune response have not been previously explored (Weber J et al 2016, McFadyen J et al 2018, Litvack M et al 2010, Agrawal A et al 2003, Whitehead A et al 1990). In the work described in the attached preprint, we show that APPs, particularly CRP, have a profound suppressive effect on adaptive immunity in melanoma patients. CRP not only diminished the proliferation and effector function of CD4+ and CD8+ T cells from melanoma patients, but it also down-regulated dendritic cell function and altered the phenotype of T cells and dendritic cells. In T cells, CRP bound to T cells and inhibited the immune synapse leading to suppression of the earliest events in T-cell receptor engagement, including calcium flux and T cell receptor signaling, resulting in a chronic state of immune suppression which has been shown to be associated with a poor outcome with the use of PD-1 blockade in melanoma and lung cancer. The RNA seq analysis suggested that CRP down- regulated cell cycle pathway genes and T cell activation genes such as CD38, ICOS and CTLA-4, indicating that CRP may act both to suppress immune synapse formation and T cell receptor signaling at the time of TCR engagement, and may also down modulate proliferation and function of T cells independent of TCR engagement.

The data presented in the attached pre-print suggest that CRP and other APPs may be responsible for a profound state of systemic immune suppression in cancer patients for both effector T cells and antigen presentation, and are consistent with previous reports that CRP and APPs are associated with a poor outcome for different cancers and with checkpoint blockade in melanoma and other cancers. Our work evaluated the impact of CRP and APPs on peripheral blood cells from melanoma patients, and did not explore the effects of CRP on neo-antigen specific T cells or immunity within the tumor microenvironment. Those studies, including an assessment of the impact of APPs on anti-tumor immunity using tumor spheroids are planned as part of an ongoing clinical trial. The role of CRP on T cell responses and resistance to PD-1 blockade has not been evaluated in murine models, and the differences in protein sequence and function of CRP in mice and humans may render such studies problematic (Whitehead A et al 1990).

CRP has been shown in mice to facilitate the opsonization of bacteria by binding to Fc gamma receptors, yet in work we performed that is described in the attached pre-print, blockade of Fc gamma receptors did not impact on the adaptive immunosuppression observed with CRP (Thomas-Rudolph D et al 2007). The levels of CRP that were

associated with suppression of T cell and dendritic cell function (10-100 micrograms per mL) in this study are observed in the serum of many patients with advanced cancer. The finding in our study that serum CRP levels are associated with response and overall survival in stage IV melanoma patients treated with nivolumab or ipilimumab further support an immune suppressive role for CRP and possibly other APPs and suggest a novel mechanism for resistance to PD-1 blockade in melanoma that nay be applicable to other cancers. CRP has been shown to alter dendritic cell maturation and function in murine models (Jimenez R et al 2018), although it has not been shown to behave similarly with human DCs, and few investigations have explored the impact of high levels of CRP on human T cells.

There are considerable data that support reduction of CRP as an anti-cancer strategy. CRP has been described as a prognostic factor for outcome in patients with melanoma, as has serum amyloid a (SAA) (Fang S et al 2015, Findeisen P et al 2009). Antibodies against IL-1β and IL-6 receptor that block liver and monocyte synthesis of CRP and other APPs have been tested in patients and are FDA-approved for a variety of indications. Tocilizumab, a humanized anti-IL-6Rα antibody that is FDA-approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and polyarticular juvenile rheumatoid arthritis, has been tested in cancer patients, to suppress the cytokine release syndrome (CRS) observed with the use of CAR-T cell therapy, and more recently for the reversal of PD-1 blockade-associated immune related adverse events (Brudno J et al 2015, Teachey D et al 2015).

The IL-1β blocking antibody canakinumab was used in a cardiac prevention trial to test the hypothesis that it could reduce the incidence of heart attack, stroke, or cardiovascular death in patients with elevated C-reactive protein, a biomarker for cardiovascular risk. There was a significant reduction in incidence of lung cancer noted in that trial (Ridker P et al 2017). Reduction in both cardiac events and lung cancer diagnoses was associated with extent of reduction of serum CRP levels (Ridker P et al 2017). There are many different explanations for the reduction in incidence of lung cancer, but the adaptive immune suppressive role for CRP suggested by our data herein suggest that a re-invigorated immune response may be at least in part responsible. The data that we have generated in the attached pre-print would support the use of tocilizumab in combination with CPI to augment its clinical effect, and based on prior clinical experience, reduce the irAEs associated with checkpoint blockade.

1.5 Rationale for the Study

Advanced tumors evade host immune responses by a variety of mechanisms systemically and by creating an immune suppressive microenvironment around the tumor. The immunomodulatory properties of interleukin-6 may in part be responsible for immune related adverse events, given the reversal of those toxicities observed with IL-6 receptor blockade in clinical practice and given the known activity of IL-6 blockade in reversing CAR-T-cell related cytokine release syndrome. Importantly, IL-6 may play a role as a chronic inflammatory mediator in raising levels of acute phase proteins synthesized by the liver and circulating cells of the myeloid lineage which have been shown to be associated with a short survival with checkpoint inhibition and which are immune suppressive. Therefore, it is felt that there is a strong rationale for combining an IL-6 receptor blocking antibody, tocilizumab, with checkpoint inhibition with ipilimumab and nivolumab in

metastatic melanoma to reduce toxicity and potentially augment the therapeutic effect of combination checkpoint inhibition.

1.6 Potential Risks & Benefits

1.6.1 Known Potential Risks

See the relevant package inserts for the three FDA approved drugs, as well as the Investigator brochure and Dear Investigator letter for Tocilizumab.

1.6.2 Known Potential Benefits

The potential benefits to subjects with study participation are improved overall progression-free and overall survival and decreased toxicity from treatment with FDA-approved ipilimumab and nivolumab. The information obtained from this research may help others with this disease in the future.

2 STUDY OBJECTIVES

2.1 Co-primary Objectives

The co-primary objectives of the study are:

- Determine the safety, tolerability, and grades 3-5 immune related toxicities of tocilizumab administered every 6 weeks up to week 24 in combination with ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a 12 week induction period, then nivolumab at 240 mg flat dose every 2 weeks in maintenance for up to 24 weeks, and nivolumab at 480 mg flat dose every 4 weeks thereafter for up to 2 years in patients with unresectable Stage III/Stage IV melanoma.
- Determine the preliminary antitumor activity of tocilizumab administered in combination with ipilimumab and nivolumab to patients with unresectable stage III or stage IV melanoma defined as overall response rate (ORR, CR + PR) at 24 weeks by RECIST 1.1

2.2 Secondary Objectives

The secondary objectives of the study are:

- Determine the preliminary antitumor activity of tocilizumab administered in combination with ipilimumab and nivolumab to patients with unresectable stage III or stage IV melanoma measured by progression-free and overall survival (Eisenhauer, E et al 2009).

2.3 Exploratory Objectives

- Determine the pharmacodynamic effect of the 3-drug combination dose regimen on biomarkers in peripheral blood samples and tumor biopsy specimens.

3 INVESTIGATIONAL PLAN

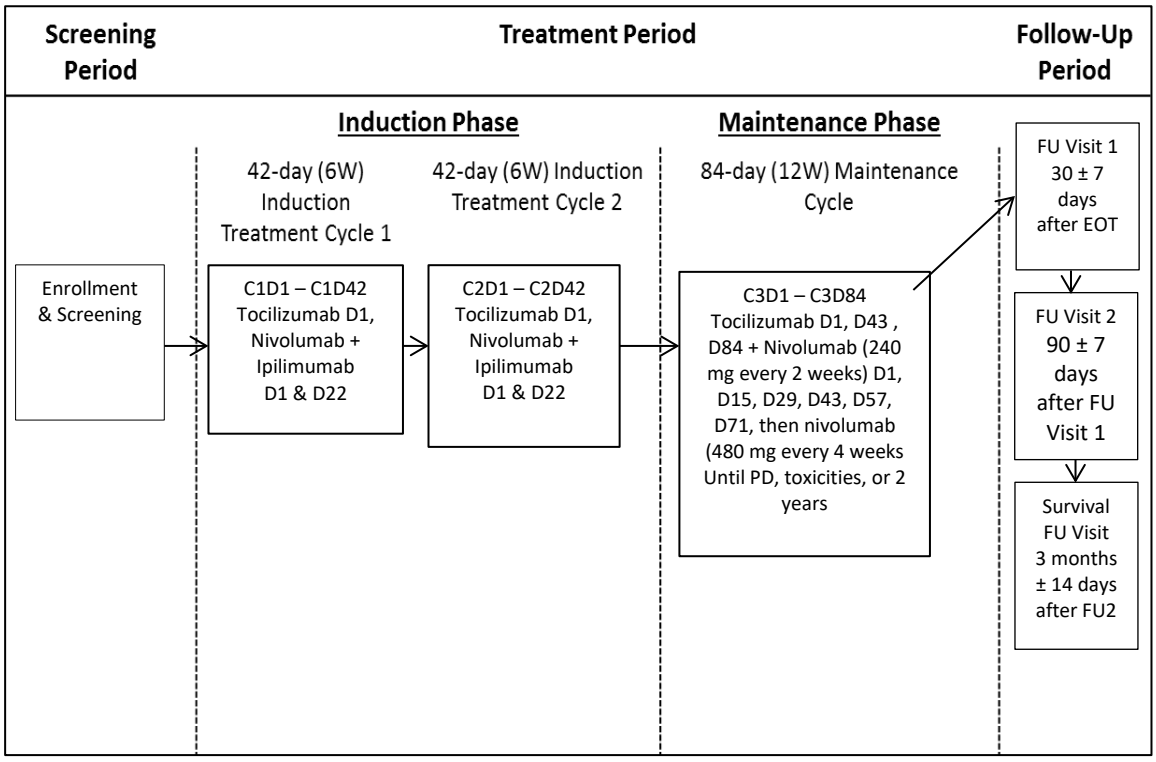
3.1 Overall Study Design and Plan: Description

In this Phase II, open-label study, the treatment period will consist of an induction phase and a maintenance phase. The induction phase consists of 2 induction treatment cycles of 42 days (6 weeks) each, of which the first cycle of 6 weeks is the DLT period. The maintenance phase consists of treatment cycles of 84 days (12 weeks) each, and may extend up to 2 years.

During the induction phase, ipilimumab will be administered for 4 induction doses (during the 2 treatment cycles) at a dose of 1 mg/kg intravenously (IV) every 3 weeks, 4 times during the 12-week induction period, concurrent with nivolumab at 3 mg/kg administered at the same interval with a 30 minute rest period between infusions. On days administered in combination, nivolumab will be administered first at a dose of 3 mg/kg, followed by ipilimumab at 1 mg/kg, and immediately followed by tocilizumab at 4 mg/kg. Nivolumab and ipilimumab will be each administered IV each over 30 minutes consecutively with a 30-minute rest period between infusions, on Days 1 and 22 of each 42-day induction treatment cycle. Tocilizumab will be administered intravenously for each 42-day induction treatment cycle.

After 12 weeks of therapy, starting at Week 13, subjects enter the maintenance phase. Tocilizumab will be administered intravenously every 6 weeks during the first 84-day maintenance treatment cycle only at 4 mg/kg. On days when administered in combination, nivolumab will be administered first, followed by tocilizumab, within 15 minutes . Nivolumab will continue to be administered IV at 240 mg flat dose every 2 weeks; i.e., at Days 1, 15, 29, 43, 57, and 71 of the 84-day treatment cycle for the first maintenance cycle until week 24, then nivolumab will be administered at 480 mg flat dose every 4 weeks to a maximum of 2 years. Subjects will continue maintenance treatment with their tocilizumab for up to 24 weeks, and their nivolumab dose regimen for up to 2 years or until progression of disease, discontinuation due to toxicity, withdrawal of consent, or any other reason as specified in Section 7.5.6 and Section 4.6.2.

A schematic of the study design is presented below in Figure 3.



Abbreviations: C = cycle; D = day; FU = follow-up; PD = progressive disease; QD = once daily; W = week.

The planned study assessments are presented in Table 2 and described below.

This study will consist of 3 periods: screening, treatment (includes induction phase and maintenance phase), and follow-up.

If de-escalation of tocilizumab from level 1 is needed, it will go to level -1 (**Table 1**). If neither co-primary endpoint is satisfied after stage 1, then we will start again at dose level 2.

3.1.1 Study Materials

- National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (ref)
- Nivolumab package insert
- Ipilimumab package insert
- Tocilizumab package insert

3.1.2 Screening Phase

- Begins by establishing the patient's initial eligibility and signing of the informed consent form (ICF).
- Patient is assessed for complete study eligibility within the required timeframe

- A pregnancy test for WOCBP should be documented within 24 hours prior to the start of the first dose of study medication. Pregnancy tests may be performed on serum or urine.
- Baseline tumor tissue must be received at NYU for programmed death ligand-1 (PD-L1) immunohistochemistry (IHC) testing and other assays in order for the patient to be treated. If the tissue specimen cannot be made available to NYU prior to the patient's first dose of the study drug, subjects are allowed to start treatment as long as there is confirmation that tissue is available and of sufficient quantity.
- The pathology reports confirming unresectable melanoma must be reviewed by the site Investigator prior to treatment.

Retesting of laboratory parameters and/or other assessments within any single screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e., the most current result prior to the first dose of study drug) and is the value by which study inclusion will be assessed, as it represents the patient's most current, clinical state.

Laboratory parameters and/or assessments are included in Table 2; Screening Procedural Outline may be repeated in an effort to find all possible well-qualified patients.

3.1.3 Treatment Phase

- Following confirmation of the participant's eligibility, the subject will receive the first doses of study medication (Day 1 of Week 1).
- On-study laboratory assessments should be drawn within 72 hours prior to dosing.
- Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every 3 weeks ± 1 week. Pregnancy tests may be performed on serum or urine.
- Treated subjects will have a clinical and radiologic disease evaluation every 12 weeks ± 7 days.
- This phase ends when the subject is discontinued early from study therapy or at a maximum of 2 years of treatment. For a complete list of reasons for treatment discontinuation, see Section 7.7.6.

3.1.4 Follow-up Phase

- Begins after 2 years of treatment or when the decision is made to discontinue a subject from study therapy.
- After completion of the first 2 follow-up visits, subjects will be followed every 3 months for survival, or by their referring physician.
- Subjects who discontinue treatment for reasons other than progression of disease will continue to have disease assessments until local, regional, or distant progression.
- Surveillance assessments should occur every 12 weeks ± 7 days during the first year after the first dose of study drug, every 12 weeks ± 14 days during the second year,

every 6 months ± 4 weeks between Year 3 through Year 5 with the last study assessment at Year 5.

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication.

The subjects will be treated in all cohorts until disease progression, unacceptable toxicity, or subject withdrawal of consent with a maximum of 2-year total duration of study medications.

The total duration of the study from the first dose of study drug to final analysis of toxicity and tolerability is expected to be 18 months.

The study will end once survival follow-up has concluded at year 5 in all patients.

3.1.5 Schedule of Assessments

The schedule of planned study assessments is shown in Table 2.

Table 2: Schedule of Assessments

Screening Phase (Day –28 to Day –1 before First Dose		Treatment Period										Follow-Up Period[a]		
		Induction Phase Cycle 1			Induction Phase Cycle 2		Maintenance Phase Cycle 3							
Study Day	**–28 to –1**	**Day 1 Wk 1**	**Day 1 Wk 4**	**Day 1 Wk 5 to 6**	**Day 1 Wk 7**	**Day 1 Wk 10**	**Day 1 Wk 13**	**Day 1 Wk 25**	**Day 1 Wk 37**	**Day 1 Wks 49 to 103**	**EOT[u]**	**FU 1**	**FU 2**	**SFU**
Informed consent	X													
Inclusion/exclusion criteria[b]	X													
Medical and surgical history	X													
Review of pathology report[c]	X													
Tumor tissue samples for biomarkers[d]	X			X[e]										
Physical examination[f,]	X	X	X		X	X	X	X	X	X	X			
Vital signs[h]	X	X	X		X	X	X	X	X	X	X			
Oxygen saturation[i]	X	X	X		X	X	X	X	X	X	X			
ECOG performance status[g]	X	X	X		X	X	X	X	X	X	X			
Baseline signs and symptoms	X													
Adverse event assessment[j]		X	X		X	X	X	X	X	X	X	X	X	X[j]
Concomitant medications review		X	X		X	X	X	X	X	X	X			
12-lead ECG[g,k]	X											X		
Hematology[,l,w]	X	X				X			X		X			
Clinical chemistry[,l,v,w]	X	X				X			X		X			
Pregnancy test for WOCBP only[m]	X	X	X		X	X	X	X	X	X				
Serology[n]	X													
Tumor assessment (CT or MRI imaging)[p,x]	X						X	X	X	X	X	X	X	X

Screening Phase (Day -28 to Day -1 before First Dose		Treatment Period										Follow-Up Period[a]		
		Induction Phase Cycle 1			Induction Phase Cycle 2		Maintenance Phase Cycle 3+							
Study Day	**–28 to –1**	**Day 1 Wk 1**	**Day 1 Wk 4**	**Day 1 Wk 5 to 6**	**Day 1 Wk 7**	**Day 1 Wk 10**	**Day 1 Wk 13**	**Day 1 Wk 25**	**Day 1 Wk 37**	**Day 1 Wks 49 to 103**	**EOT[u]**	**FU 1**	**FU 2**	**SFU**
Blood (serum) and urine for exploratory biomarker assessments and Peripheral Blood Mononuclear cells (PBMCs) [q]	X	X			X				X					
Peripheral Blood Mononuclear cells (PBMCs)	X	X			X				X					
Biopsies of affected organs (OPTIONAL)[s]														
Administration of tocilizumab[r]		X	X[r]				X							
Administration of nivolumab[r]		X	X		X	X	X	X	X	X				
Administration of ipilimumab[r]		X	X		X	X								

Abbreviations: AE = adverse event; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FU = follow-up visit; MRI = magnetic resonance imaging; NYU = New York University; PD-L1 = programmed death ligand-1; SAE = serious adverse event; SFU = survival follow-up visit; WOCBP = women of child-bearing potential.

[a] Follow-up visit 1 (FU1) = 30 days (± 7 days) from end of treatment (EOT), Follow-up visit 2 (FU2) = 90 days (± 7 days) from FU1. First SFU is 12 weeks (±14 days) after FU2. Phone contacts during the SFUs are only allowed at time periods between surveillance assessment visits. Surveillance assessments with imaging and exam evaluations should occur every 12 weeks ± 7 days during the first year after the last dose of study drug was administered, every 12 weeks ± 14 days during the second year, every 6 months ± 4 weeks between Year 3 and Year 5, with the last assessment at Year 5.

[b] All inclusion/exclusion criteria should be assessed during the screening and confirmed before the first dose of study drug.

[c] Patients must have unresectable Stage IIIb/c or Stage IV melanoma. The pathology report must be reviewed and dated by the Investigator before treatment.

[d] Sufficient tumor tissue from a prior resected site of disease (archived) will be collected for biomarker analysis. Please reference the Laboratory Manual.

[e] On-treatment biopsies (optional) will be collected during the induction cycle 1 between Days 35 and 42 (± 3 days).

[f] Height and weight are to be measured at the screening visit. Thereafter, only weight is measured.

[g] Initial biomarker testing must be performed within 14 days prior to the first dose of study drug. Subsequent EKG testing will only be performed if clinically indicated, or at the FU1 visit

[h] Vital signs include temperature, systolic and diastolic blood pressure, heart rate, and body temperature.

[i] Oxygen saturation is measured by pulse oximetry at rest, and must be done before dosing.; pulse oximetry on exertion will be performed only if there are respiratory symptoms, fatigue and/or radiographic abnormalities suggestive of pneumonitis

[j] Patients will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication unless other therapy begins during that period.

[k] Single 12-lead ECGs will be collected at screening, and at FU1.

[l] Hematology and chemistry testing are done at each treatment visit, every three weeks during the first 12 weeks of induction, and every 2 weeks from weeks 12-24, then every 4 weeks until 2 years, toxicity or progression on site or at a local laboratory. Refer to Section 6.7.1 and Section 6.7.2, respectively, for individual tests to be included. Laboratory testing does not need to be repeated on Day1, Week 1 if performed within 14 days before the first dose.

[m] Pregnancy testing must be performed within 24 hours before the initial dose of study drug, and then every 3 weeks ± 1 week. Pregnancy tests may be performed on serum or urine.

[n] Serology testing is done on site or at a local laboratory. Refer to Section 6.7.3 for individual tests to be included. Serology testing, if needed, must be performed within 28 days before the first dose of study drug. Laboratory testing does not need to be repeated if performed within 14 days before first dose.

[p] Tumor assessments are performed by CT scan on the chest, abdomen, pelvis, and all other known sites of disease, and brain MRI (brain CT is allowable if MRI is contraindicated).

[q] Serum and urine samples for exploratory biomarkers should be taken before dosing at Week 1, 7, and 37, and upon occurrence of ≥ Grade 3 drug-related AEs and/or laboratory abnormalities regarded as a drug-related SAE, when clinically safe and feasible.

[r] First dose to be administered within 3 business days of initiation. Subsequent doses may be administered within 3 days before or after the scheduled date if necessary. Ipilimumab is only given during the Induction Phase, at three week intervals, four times. Nivolulab is given every 3 weeks for the first 4 induction doses, then every 2 weeks for weeks 12-24 at 240 mg fixed dose, then every 4 weeks at a fixed dose of 480 mg until 2 years (week 103), toxicity or progression. Tocilizumab is given D1 of the 2 induction cycles, then day 1 and D43 of the first maintenance cycle only, at 42 day intervals for a total of 24 weeks up until week 25.

[s] Upon occurrence of a ≥ Grade 3 drug-related AE and/or any lab abnormality regarded as a drug related SAE, a biopsy of the affected organ(s) may be optionally collected.

[t] End of treatment occurs at the time a patient discontinues therapy due to progression-of disease, toxicity or refusal to continue, or when a patient reaches 2 years of therapy

[u] Serum lipid panel/profile will be performed at baseline, week 4, and then weeks 12, 24 and 36

[v] The CBC and CMP will be checked before administration of any protocol drugs on this trial including tociluzumab.

[w] Scans will be done every 3 months on treatment for up to 3 years, then every six months thereafter

4 SELECTION OF STUDY POPULATION

4.1 Number of Planned Subjects

Safety evaluation and efficacy: This is a Phase II open label optimal Simon two-stage design trial. A total of 67 patients allows sufficient number of patients to assess the grades 3-5 irAE toxicity rates of the triple drug combination, and provide an estimate of the overall response rate by RECIST 1.1.

4.2 Inclusion Criteria

1. Patients must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.
2. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.
3. All patients must be either Stage IIIb/c/d or Stage IV melanoma according to the American Joint Committee on Cancer (AJCC) (8th edition) and have histologically-confirmed melanoma that is felt to be surgically unresectable in order to be eligible. Please refer to the AJCC 8th edition Cancer Staging Manual for a description of tumor, lymph node, metastasis, and staging.
    - All melanomas, except ocular/uveal melanoma, regardless of primary site of disease will be allowed; mucosal melanomas are eligible.
    - Patients must not have received prior anticancer treatment for metastatic disease (for example, but not limited to, systemic, local, radiation, radiopharmaceutical).
    - Exceptions: Surgery for melanoma and/or post-resection brain radiotherapy (RT) if CNS metastases and adjuvant RT for locoregional disease after resection and/or prior treatment with adjuvant IFN-alpha, dabrafenib and trametinib, pembrolizumab, ipilimumab or nivolumab (as described in Exclusion Criterion 8).
    - All patients must have their disease status documented by a complete physical examination and imaging studies within 4 weeks prior to the first dose of study drug. Imaging studies must include computerized tomography (CT) scan of chest, abdomen, pelvis, and all known sites of resected disease in the setting of Stage IIIb/c/d or Stage IV disease, and brain magnetic resonance imaging ([MRI]; brain CT is allowable if MRI is contraindicated).
    - The complete set of baseline radiographic images must be available before treatment initiation.
4. Prior treatment with adjuvant IFN-alpha, adjuvant ipilimumab and/or nivolumab or pembrolizumab or dabrafenib and trametinib are allowed at any time; that is, a patient may have relapsed with unresectable disease during or at any time after receiving adjuvant therapy
5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.
6. Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be treated, a patient must have tissue available for PD-L1 expression analysis by IHC and other assays obtained within 6 months of starting treatment. If insufficient

tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and/or slides) for the biomarker analysis is required.

7. Prior treated CNS metastases must be without MRI evidence of recurrence for at least 4 weeks after treatment. Patients must be off immunosuppressive doses of systemic steroids (≥ 10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration, and must have returned to neurologic baseline status postoperatively.
    a. The 4-week period of stability is measured after the completion of the neurologic interventions (i.e., surgery and/or radiation).
8. In addition to neurosurgery to treat CNS metastases, adjuvant radiation after the resection of CNS metastasis is allowed. Immunosuppressive doses of systemic steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 14 days before study drug administration.
9. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration.
10. All baseline laboratory requirements will be assessed and should be obtained within 14 days of the first dose of study drug. Screening laboratory values must meet the following criteria:
    - WBCs ≥ 2000/µL
    - Neutrophils ≥ 1500/µL
    - Platelets ≥ 100 × 10^3/µL
    - Hemoglobin ≥ 9.0 g/dL
    - Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
    - AST ≤ 1.5 × ULN
    - ALT ≤ 1.5 × ULN
    - Total bilirubin ≤ 1.5 × ULN (except patients with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)
11. Patient Re-enrollment: This study permits the re-enrollment of a patient that has discontinued the study as a screen failure (i.e., patient has not been dosed/has not been treated). If re-enrolled, the patient must be re-consented and satisfy all eligibility criteria.
12. Males and females ≥ 18 years of age
13. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG] hormone) within 24 hours prior to the start of study drug during induction phase at each scheduled visit and during the maintenance phase every 4 weeks while on treatment.

14. Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle). The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. WOCBP should therefore use an adequate method to avoid pregnancy for a total of 23 weeks post treatment completion (Section 4.5).
15. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. (Refer to Section 4.5).

4.3 Exclusion Criteria

1. Patients with active or history of steroid-requiring non-infectious pneumonitis.
2. Patients who have previously discontinued immunotherapy due to an immune-mediated adverse reaction, regardless of grade
3. Patients with carcinomatosis meningitis or a history of current ocular/uveal melanoma are excluded.
4. Patients with previous nonmelanoma malignancies are excluded unless a complete resection or remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include, but are not limited to, nonmelanoma skin cancers, in situ bladder cancer, in situ gastric cancer or gastrointestinal stromal tumor, in situ colon cancers, in situ cervical cancers/dysplasia, or breast carcinoma in situ).
5. Patients with active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the Principal Investigator be consulted prior to signing informed consent.
6. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
7. Prior therapy for melanoma with the following exceptions which are allowed: 1) surgery for the melanoma lesion(s), 2) adjuvant RT after neurosurgical resection for CNS lesions or for resected locoregional disease, and 3) prior adjuvant IFN-alpha, ipilimumab and nivolumab (see qualifier below).
8. Treatment directed against the melanoma (e.g., chemotherapy, targeted agents, biotherapy, limb perfusion) that is administered after a prior complete resection other than adjuvant radiation after neurosurgical resection or resection of locoregional disease and IFN-alpha,

ipilimumab and/or nivolumab, pembrolizumab and dabrafenib and trametinib for resected melanoma.

9. Any of the following laboratory abnormalities:
   - ANC < 1,500/µL or WBC < 2,000 µL
   - Platelet count < 100,000/µL
   - Hematologic growth factors are not allowed at screening or during the first cycle of treatment
   - Hemoglobin < 9 g/dL (< 5.5 mmol/L; previous RBC transfusion is permitted)
   - Creatinine > 1.5 × ULN
   - AST or ALT > 1.5 × ULN. For patients with liver metastasis AST or ALT > 3 × ULN
   - Serum total bilirubin > 1.5 mg/dL or > 3 × ULN for patients with hereditary benign hyperbilirubinemia
10. Corrected QT interval using Fridericia's formula value > 480 msec at screening; family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy at screening; previous history of drug-induced QTc prolongation or the need for treatment with medications known or suspected of producing prolonged QTc intervals on electrocardiogram (ECG).
11. Congestive heart failure (New York Heart Association Class III or IV), myocardial infarction within 12 months before starting study treatment, or unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris.
12. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the Investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the patient to receive protocol therapy.
13. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections
14. Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
15. Positive QuantiFERON TB test , history of tuberculosis, or active TB infection without at least 4 weeks of adequate therapy for TB.
16. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (include uncontrolled diabetes mellitus) or gastrointestinal disease (including complicated diverticulitis, ulcerative colitis, or Crohn's disease.)
17. Immunization with a live or attenuated vaccine within 4 weeks of baseline.
18. Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome
19. Known hypersensitivity to monoclonal antibodies
20. History of diverticulitis in the last 10 years
21. History of Grade ≥ 3 allergy to human monoclonal antibodies

22. Prisoners or patients who are involuntarily incarcerated
23. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
24. Pregnant or nursing women
25. Psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

4.4 Inclusion of Women and Minorities

Both women and men of all races and ethnic groups are eligible for this trial.

4.5 Women of Childbearing Potential

Women of childbirth potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The washout periods below are suggested guidelines and the Investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

4.6 Removal of Patients from Therapy or Assessments

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Subject’s request to stop study treatment
- Documented progression of disease (local, regional or distant) by immune-related response criteria (irRC)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient
- Termination of the study by BMS and/or Genentech

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 7.7.6).

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 3.1.4. The only exception to this requirement is when a patient withdraws consent for all study procedures including post treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the patient's completion of the study, the reason for the discontinuation must be documented in the patient's medical records and entered on the appropriate CRF page.

Pregnancy

In the case of pregnancy, the Investigator must immediately notify the main site of the trial, NYU, and the sponsor will report to BMS Worldwide Safety and Genentech Drug Safety of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the Investigator and the BMS Medical Monitor/designee must occur.

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

4.7 Post Study Follow-up

In this study, toxicity defined as grades 3-5 treatment-related irAEs is a primary endpoint, and overall response (ORR) rate is the clinical co-primary endpoint. Post-study follow-up is of critical importance and is essential to preserving patient safety and the integrity of the study. Patients who discontinue study drug must continue to be followed for collection of outcome data as required until death or the conclusion of the study, with survival follow-up for a minimum of 5 years.

4.8 Withdrawal of Consent

Patients who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study drug only

or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

4.8.1 Lost to Follow-up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death.

The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the patient's medical records.

5 INVESTIGATIONAL PRODUCTS

5.1 Investigational Products Administered

Study drugs include all investigational [Medicinal] Products (tocilizumab, ipilimumab and nivolumab).

At the end of the study period, Bristol-Myers Squibb Company and Genentech Inc. will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

5.1.1 Investigational Product Tocilizumab

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.
Intravenous Infusion tocilizumab injection is supplied as a sterile, preservative-free solution for further dilution prior to intravenous infusion at a concentration of 20 mg/mL. tocilizumab is a clear, colorless to pale yellow liquid, with a pH of about 6.5. Single-dose vials are available for intravenous administration containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of tocilizumab. Injectable solutions of tocilizumab are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol per L phosphate buffer), polysorbate 80 (0.5 mg per mL), and sucrose (50 mg per mL).

The investigational product tocilizumab should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that the non-investigational products are only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

Patients will take tocilizumab intravenously at a dose of 4 mg/kg administered in combination with ipilimumab and nivolumab. If any intermediate doses and schedules of tocilizumab are felt to be indicated after consultation with the investigators, BMS, Genentech Inc. and the FDA, the IRB will be informed of any implementation of intermediate doses.

5.1.2 Investigational Study Drugs Ipilimumab and Nivolumab

Investigational, standard of care products may consist of the following as shown in Table 3:

Table 3: Investigational Study Drugs (Standard of Care)

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Primary Packaging/ Appearance	Storage Conditions (per label)

Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	Per IB asnd PI	Open-label[b]	10 mL/vial	Store at 2 to 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg or 50 mg (5 mg/mL)	Per IB and PI	Open-label[b]	40 mL/vial	Store at 2 to 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	Non-IMP	Open-label	Various (local commercial product)	As per active PI
5% Dextrose for Injection	N/A	Non-IMP	Open-label	Various (local commercial product)	As per active PI

Abbreviations: IMP = investigational medicinal product; IP = investigational product; N/A = not applicable.

[a] Nivolumab injection drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution. Its appearance is a clear to opalescent, colorless to pale yellow liquid which may contain particles. Nivolumab is secondary packaged in 10-mL Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.

[b] The term "open label" refers to the medication as it is upon receipt at the pharmacy.

If nivolumab is stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab package insert.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative site if available and permitted by local regulations. Solutions used as diluent or placebo (i.e., 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative site if available and permitted by local regulations.

The Investigator is responsible for ensuring that the noninvestigational products are stored under the appropriate environmental conditions (temperature, light, and humidity). The Investigational products must be dispensed only from official study sites by authorized personnel according to local regulations.

5.2 Identity of Investigational Product

5.2.1 Formulation and Packaging

Tocilizumab

Medication labels comply with the legal requirements of the United States and will be printed in the languages required in the countries in which the study is conducted.

5.2.2 Drug Storage and Accountability

Tocilizumab liquid should be stored protected from light, at suggested range is 36--48°F, 2-8°C) according to instructions on the label. The storage area should be secure with limited access and monitored for temperature using a calibrated thermostat. Available stability data support ≥ 12-months shelf-life when stored under the above conditions, depending on vial strength.

All study treatment supplies will be accounted for in the drug accountability inventory forms using locally approved forms that include all required information. The drug accountability

inventory forms must identify the study drug, including batch or lot numbers and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

5.2.3 Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.4 Medication Compliance

Study site personnel should provide each patient with written dosing information for Tocilizumab and review it with the patient during clinic visits.

5.2.5 Destruction

At the end of the study, all unused Tocilizumab drug supplies must be destroyed in accordance with local Standard Operating Procedure provided by the Sponsor (NYU), or returned to the Sponsor.

5.2.6 Administration

Tocilizumab will be administered intravenously over 30 minutes at 4 mg/kg in 42 day cycles. The starting dose for tocilizumab is 4 mg/kg. The dose may be deescalated depending on observed safety.

Tocilizumab for infusion will be supplied by Genentech Inc. to NYU, The Angeles Clinic and Dana Farber Cancer Institute investigational pharmacies in appropriately sized vials for intravenous administration. Dose preparation instructions are provided in detail in the investigational brochure and package inserts for all three drugs.

The label attached to each bottle will contain the appropriate information, including product name and amount, lot number, directions for storage, date of manufacture, name of Sponsor, and the region-specific regulatory information.

Study-drug labels will not contain any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

5.2.7 Storage and Dispensing

The Investigator should ensure that the study drugs tocilizumab, ipilimumab and nivolumab are stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information, the IB, per local regulations, and as determined by BMS and Genentech. If concerns regarding the quality or appearance of the study drug(s) arise, the study drug(s) should not be dispensed and contact BMS and/or Genentech immediately.

Please refer to the current version of the IB and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for tocilizumab**.**

It is the responsibility of the Investigator to ensure that drug product is only dispensed to study patients.

Study drugs (tocilizumab, nivolumab and ipilimumab) will be stored in accordance with the package inserts. Please refer to the current version of the investigator brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for tocilizumab, nivolumab and ipilimumab.

Product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

Infusion-related supplies (e.g., IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will be purchased locally if permitted by local regulations.

The NYU, The Angeles Clinic and Dana Farber investigational pharmacists or their delegate will obtain treatment assignment and prepare investigational drug.

On days administered in combination, nivolumab will be administered first at a dose of 3 mg/kg, followed by ipilimumab at 1 mg/kg, and immediately followed by tocilizumab at 4 mg/kg. The infusion duration for tocilizumab, nivolumab and for ipilimumab is 30 minutes each .

If the study drug(s) are 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.

It is the Sponsor Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.2.8 Destruction of Study Drugs

For this study, study drugs (those supplied by BMS, Genentech or sourced by the Investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS and/or Genentech upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the principal investigator will make arrangements for return of study drug.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.2.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug tocilizumab that was supplied by Genentech must be returned to Genentech, and any study drug ipilimumab and/or nivolumab that was supplied by BMS must be destroyed. The return of study drug will be arranged by the responsible Study Monitor.

It is the principal Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.3 Method of Assigning Subjects to Treatment

After the participant's initial eligibility is established and informed consent has been obtained, the patient must be enrolled into the study. Every patient that signs the ICF must be assigned a patient number. The Investigator or designee will register the patient for enrollment by following the enrollment procedures established by the Perlmutter Clinical Trials Office. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth
- Race/Ethnicity
- Zip Code
- AJCC Stage and M classification
  - Stage IIIb/c/d
  - Stage IV M1a-M1b

– Stage IV M1c/d

Once enrolled, enrolled patients that have met all eligibility criteria (the required tumor tissue received by the NYULH, Angeles Clinic and Dana Farber Pathology laboratories) will be ready to be treated.

5.4 Selection and Timing of Doses in the Study

When study drugs (tocilizumab, ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. On days administered in combination, nivolumab will be administered first at a dose of 3 mg/kg, followed by a 30-minute rest period, followed by ipilimumab at 1 mg/kg, and immediately followed by tocilizumab at 4 mg/kg.

Intravenous tocilizumab will be dosed at 4 mg/kg every 6 weeks at D1 of the first 2 induction cycles, and at D1, D43 and D84 of the first maintenance cycle only for a total of 5 doses.

Patients may be dosed up to ± 3 days before or after the scheduled date if necessary.

Vital signs will be taken before dosing of each drug.

5.5 Dosing Schedule

The dosing schedule is described in Table 4. Weight should be used to calculate the dose and if the weight differs 5% or10% (depending on local institutional standards) from baseline, the dose should be recalculated.

Table 4: Dosing Schedule

<table>
<tr><th></th><th>Day 1
Week 1</th><th>Day 1
Week 4</th><th>Day 1
Week 7</th><th>Day 1
Week 10</th><th>Day 1
Week 13</th><th>Day 1
Weeks 25, 37, 49, 52</th></tr>
<tr><td rowspan="3">Nivolumab
+
Ipilimumab
+
Tocilizumab</td><td>3 mg/kg
nivolumab</td><td>3 mg/kg
nivolumab</td><td>3 mg/kg
nivolumab</td><td>3 mg/kg
nivolumab-</td><td rowspan="3">240 mg
nivolumab
Every two weeks for 12 weeks
+
4 mg/kg
Tocilizumab
A: Weeks 19 and 25</td><td rowspan="3">240 mg
nivolumab
Every two weeks for each 12 week cycle
+
4 mg/kg
Tocilizumab[a]

a: Weeks 19 and 25</td></tr>
<tr><td>1 mg/kg
ipilimumab</td><td>1 mg/kg
ipilimumab</td><td>1 mg/kg
ipilimumab</td><td>1 mg/kg
ipilimumab</td></tr>
<tr><td>4 mg/kg
Tocilizumab</td><td>-</td><td>4 mg/kg
Tocilizumab</td><td></td></tr>
</table>

If a patient cannot receive a dose of drugs within 3 days of its scheduled administration date, the dose should be completely omitted. When the patient is able to reinitiate treatment, dosing should resume at the time of the next scheduled dose. Missed doses will not be replaced.

Antiemetic pre-medications should not be routinely administered prior to dosing of drugs. See Section 7.12.7 for premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

5.6 Blinding

There is no blinding in this study.

5.7 Previous and Concomitant Therapy

5.7.1 Prohibited and/or Restricted Medication/Therapy

The following medications are prohibited during the treatment and follow-up phases (before recurrence) of the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.7.2).
- Any concurrent anti-neoplastic therapy (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or standard or investigational agents for treatment of melanoma).

Antiemetic pre-medications should not be routinely administered before dosing of drugs. See Section 7.12.7 for premedication recommendations following a nivolumab- or ipilimumab-related infusion reaction.

5.7.2 Permitted Therapy

Patients are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted even if > 10 mg daily prednisone (or equivalent). A brief course (< 7 days) of corticosteroids for prophylaxis (e.g., for contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Intravitreal injections of vascular endothelial growth factor inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

5.7.3 Premedication for Nivolumab or ipilimumab

There will be no routine pre-treatment for the three antibodies in this trial, but if a grade 1 or 2 infusion reaction occurs to any of the antibodies, then pre-treatment will be carried out according to section 7.12.5.2 on page 69.

5.7.4 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

Study center pharmacy personnel will prepare individual patient doses to be taken during scheduled study center visits.

6 STUDY PROCEDURES/EVALUATIONS

6.1 Medical History

At screening, a medical history will be obtained to capture relevant underlying conditions, both past and ongoing concurrent medical conditions.

6.2 Physical Examinations

A complete physical examination will be performed according to Table 2. The screening visit examination should include height as well as weight; however, at subsequent visits, only weight needs to be measured. Physical examination should be performed within 72 hours before dosing. Physical examinations are also to be performed as clinically indicated.

6.3 Vital Signs

Vital signs (diastolic and systolic blood pressure, heart rate, and body temperature) will be performed as noted in Table 2. Vital signs should also be taken as per institutional standard of care before, during, and after dosing. Vital signs will be taken in the same position (supine or sitting) at each visit.

6.4 Oxygen Saturation by Pulse Oximetry

Oxygen saturation by pulse oximetry should be obtained prior to each dosing of combination nivolumab + ipilimumab +tocilizumab treatment, nivolumab with tocilizumab treatment, nivolumab alone, and at any time a patient has any new or worsening respiratory symptoms. Oxygen saturation by pulse oximetry at rest should be obtained at each time point before dosing as noted in Table 2. If patients have respiratory symptoms and/or fatigue and/or have any radiographic abnormalities consistent with pneumonitis, accurate recording and documentation of oxygen saturation at rest and on exertion, i.e. 2 different activity levels, will be performed, and is important because drug-related pulmonary toxicity can present initially as lower than baseline oxygen saturation. The extent of the exertion should be based on the judgment of the Investigator, but should remain consistent for each individual patient throughout the study. If the patient's status changes, the Investigator can alter the extent of exertion based on his/her medical judgment. If a patient shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (e.g., dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately further evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Prescribing Information in the investigational brochure and the package insert.

6.5 Electrocardiograms

Single 12-lead ECGs will be performed at screening (i.e., within 14 days before receiving the first dose of study drug), and at the end-of-treatment visit. Additional ECGs may be performed at any time point at the Investigator's discretion.

6.6 Concomitant Medications

Concomitant medications will be collected from within 14 days before receiving the first dose of study drug through the study treatment period and follow-up visits 1 and 2 as noted in Table 2

6.7 Clinical Laboratory Evaluation

The hematology, clinical chemistry, lipid panel/profile and serology assessments will be done by local laboratories according to the time points specified in Table 2. Baseline blood samples at screening should be done within 14 days prior to the first dose of study drug. Laboratory tests do not need to be repeated if performed within 14 days prior to the first dose. Additional measures not listed here including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g., suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible. If hemoglobin levels are < 10 g/dL, blood will *only* be drawn for safety assessment, and will *not* be drawn for biomarker assessment.

6.7.1 Hematology

Hematology assessments done locally will include a complete blood count with differential, which includes a hematocrit, hemoglobin, WBC count, platelet count, RBC count, and mean corpuscular volume. These local laboratory assessments should be done within 72 hours prior to dosing.

6.7.2 Clinical Chemistry

Clinical chemistry assessments will include LFTs (ALT, AST, total bilirubin, and alkaline phosphatase), carbon dioxide, albumin, Gamma-glutamyl transferase GGT, phosphorus, blood urea nitrogen, uric acid, total protein, creatinine, calcium, magnesium, sodium, potassium, chloride, lactate dehydrogenase, glucose, amylase, lipase, TSH, free thyroxin, and free triiodothyronine, which must be initially performed within 14 days before the first dose and within 72 hours before dosing for other time points specified in Table 2.

6.7.3 Serology

Only if indicated, serology assessments will include hepatitis B and hepatitis C testing (hepatitis B virus surface antigen, hepatitis C virus antibody or RNA). These baseline serology tests should be assessed within 28 days before the first dose of study drug is administered as specified in Table 2.

6.7.4 Pregnancy Testing

Pregnancy tests (done locally, using serum or urine) must be performed on females of childbearing potential at screening, within 24 hours before the initial administration of study drug at baseline, during induction phase at each scheduled visit and during maintenance phase every 4 weeks while on treatment.

Females will be assessed as being of childbearing potential or not of childbearing potential and will undergo pregnancy testing as described below:

Pregnancy testing for WOCBP must be performed within 24 hours before the initial administration of study drug at baseline and then every 3 weeks (± 1 week) during the treatment phase. Serum or urine may be used for pregnancy testing.

- Females of childbearing potential include all females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal, and those who do not qualify for the females not of reproductive potential category. Females of childbearing potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously (1 highly effective form of contraception – tubal ligation, intrauterine device, hormonal birth control pills, injections, hormonal patches, vaginal rings, or implants) or partner's vasectomy and 1 additional effective contraceptive method: male latex or synthetic condom, diaphragm, or cervical cap.
- Females not of reproductive potential include females who have been in natural menopause for at least 24 consecutive months or who have had a hysterectomy and/or bilateral oophorectomy.
- Females of childbearing potential must agree to use adequate contraceptive measures until 5 months after last study drug is taken.

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6.7.5 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at each study visit according to Table 2 and within 72 hours before dosing. Patient ECOG performance status will be assessed as indicated in Table 5.

Table 5: Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

7 STUDY ENDPOINTS AND ASSESSMENTS

7.1 Co-Primary Endpoints:

- To determine the grades 3-5 treatment related irAEs by week 24 when tocilizumab at 4 mg/kg every 6 weeks for 5 doses is administered in combination with ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a 12-week induction period, then nivolumab is administered at 240 mg flat dosing every 2 weeks in maintenance for up to 1 year in subjects with unresectable Stage III/Stage IV melanoma.
    - Safety will be measured by physical examinations, vital sign measurements, ECOG performance status evaluations, AE assessments, laboratory testing, ECGs, oxygen saturation, and concomitant medications.
- Overall response (CR + PR) by week 24 to study treatment will be measured by RECIST 1.1

7.2 Secondary Endpoint:

- Progression-free survival will be assessed.
- Overall survival will be assessed

7.3 Exploratory Endpoints:

- Biomarkers will be measured in peripheral blood and in tumor specimens to examine associations with clinical endpoints.

7.4 Efficacy Endpoints:

7.4.1Efficacy Endpoint Based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Objective Response Rate (ORR) is defined as the total number of patients whose best response outcome is a CR or PR by week 24 divided by the total number of evaluable patients.

Disease Control Rate (DCR) is defined as the total number of patients whose best response outcome is a complete response (CR) or partial response (PR), or SD divided by the total number of evaluable patients.

Progression-Free Survival (PFS): is defined for each patient as the time from first dosing to the first observation of disease progression or death due to any cause. If a patient has not progressed or died at the time of analysis, PFS will be censored on the date of the last disease assessment. Patients who do not have any tumor assessment on treatment will be censored on the day of the first dose.

Duration of Overall Response: will be computed for all patients whose best response is either a PR or CR and is calculated from the time the measurement criteria are met for PR or CR, whichever is recorded first, until the date of documented PD or death.

Duration of Disease Control: will be computed for the patients who had ORR outcome of CR, PR, or SD and is calculated from the beginning of treatment until the time of documented disease progression.

Overall Survival: is defined for each patient as the time from first dosing to death due to any cause. If a patient has not died at the time of analysis, OS will be censored as of their last known date alive (i.e. last time patient was contacted for any reason in the study). Patients who do not have any tumor assessment on treatment be followed up for OS, and their date of death will be incorporated into the OS analysis.

Appendix 1 contains a quick reference guide to using RECIST 1.1.

7.4.2 Efficacy Endpoint Based on Immune-Related Response Criteria (irRC)

Immune Related Best Overall Response (irBOR) is the best irRC designation over 6 months, recorded between the date of first dose until the last tumor assessment prior to subsequent therapy (except for local palliative RT for painful bone lesions) for the individual patient in the study. Immune-related complete response (irCR) or immune-related partial response (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.

Immune-related Response Rate (irRR) is defined as the proportion of response evaluable patients whose irBOR outcome is irPR, irCR.

Immune-related Disease Control Rate is defined as the proportion of the response evaluable patients whose irBOR outcome is irPR, irCR, or immune-related stable disease (irSD).

Immune-related Progression-Free Survival (irPFS) is defined as the time between the first dosing date and the date of immune-related progressive disease (irPD) or death, whichever occurs first. For patients with no recorded post-baseline tumor assessment, irPFS will be censored at the day of first dose. A patient who dies without reported irPD will be considered to have progressed on the date of death. For those who remain alive and have no irPD, irPFS will be censored on the date of last evaluable tumor assessment. Patients who do not have any tumor assessment on treatment will be censored on the day of the first dose.

Duration of Immune-related Overall Response: will be computed for all patients whose irBOR outcome is either an irPR or irCR and is calculated from the time the measurement criteria are met for irPR or irCR, whichever is recorded first, until the date of documented PD or death by irRC.

Duration of Immune-related Disease Control: will be computed for the patients who had irBOR outcome of irCR, irPR, or irSD and is calculated from the beginning of treatment until the time of documented disease progression by irRC.

Appendix 2 contains a summary of the irRC assessment.

7.5 Efficacy Variables and Assessments

7.5.1 Disease Assessments

Disease assessments will take place in accordance with Table 2. Baseline disease assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. This includes a CT scan of chest, abdomen, pelvis, and all known sites of disease, and a brain MRI (brain CT allowable if MRI is contraindicated). Patients will be evaluated for tumor burden until local, regional, or distant recurrence (whichever comes first) by irRC beginning 12 weeks (± 7 days) relative to the first dose of study treatment, and will continue to have disease assessments every 12 weeks (± 7 days) for the first 12 months. After 12 to 24 months after receiving the first dose of study drug, efficacy assessments should be every 12 weeks (± 14 days). After 24 months until Year 5 after the first dose of study treatment, efficacy assessments should be performed every 6 months (± 4 weeks). CT scans will be performed every 3 months on treatment, then every 6 months after 3 years which is standard of care in stage 4 melanoma.

Progression is defined as an increase in the sum of the longest unidimensional diameters of the 5 measurable lesions defined at baseline beyond 20% from baseline or the lowest point at any time during treatment. The appearance of 1 or more new melanoma lesions, which can be local, regional, or distant in location does not constitute progression; rather the longest unidimensional diameters of all new lesions should be added into the sum to determine progression. Progression should be verified not less than 4 weeks after the first evaluation that showed it.

7.5.2 Measurable Disease per RECIST 1.1

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan (CT/MRI scan slice thickness no greater than 5 mm); PET-CT may be utilized if the CT parameters are satisfied above.
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest x-ray

Malignant lymph nodes: to be considered pathologically enlarged and measurable per RECIST 1.1, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

If the measurable disease is restricted to a solitary lesion (visceral or nodal), its neoplastic nature must be confirmed either by cytology/histology or by lesion progression certified on the next CT/MRI examination.

7.5.3 Nonmeasurable Disease per RECIST 1.1:

Nonmeasurable lesions include all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 and < 15 mm on the short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note:

- Cutaneous relapses occurring beyond the periphery of the previous surgical bed (i.e., over 2 cm) are considered distant metastases.
- Node relapses occurring beyond the anatomical compartment of the dissected basins are considered distant metastases.
- Node relapses in nodal basins situated in a different anatomical compartment or beyond the previously dissected basin or in 2 nodal basins (even if contiguous [i.e., 2 pelvic nodal basins, 2 mediastinal nodal basins]) are considered distant metastases.

7.5.4 Methods of Measurements

CT and MRI are an essential part of the work-up to establish response or progression. Conventional CT with IV contrast and MRI gadolinium should be performed with contiguous cuts of 10 mm or less slice thickness. Spiral CT should be performed using a 3-mm or 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis while head and neck tumors and those of the extremities usually require specific protocols. In each institute, the same technique for CT/MRI should be used to characterize each new lesion.

Patients allergic to contrast media may have a CT performed without contrast after discussion and agreement with the Principal Investigator.

PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.

Histological or cytological evidence of progression should be attempted in all cases except for brain metastases when safe and clinically feasible.

Tumor markers or auto-antibodies alone cannot be used to assess recurrence.

In the case of clinically detected new lesions that occur during the study:

- Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
- Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of a pathology report, lesion recurrence will be documented with a CT scan/MRI.

7.6 Date of Progression

The first date when progression was observed is taken into account regardless the method of assessment. Therefore, progression will be declared for any lesion when:

- Only imaging was performed and progression confirmed.
- Only pathology was done and malignancy confirmed in a new lesion (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions).
- Both pathology and imaging were done and progression/malignancy confirmed. In this case, the date of whichever examination comes first is considered the date of progression.

7.7 Pharmacodynamic Biomarker Assessments

A variety of factors that could potentially predict clinical response and incidence of AEs to nivolumab + ipilimumab + tocilizumab will be investigated in peripheral blood and in tumor specimens taken from all patients prior to treatment and as outlined in Table 2. Data from these investigations will be evaluated for associations with ORR rate, and PFS and/or safety (AE) data. In addition, analyses of markers will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements and/or institutional policies) to assess biomarkers associated with melanoma or immunotherapy treatment.

7.8 Biomarker Endpoints

Baseline (pretreatment) and other measures of peripheral blood, urine and intra-tumoral immune responses will be analyzed to examine associations with clinical endpoints. In peripheral blood, baseline levels of: 1) absolute lymphocyte count; 2) serum and urine cytokines; 3) T-cell subsets, their phenotype, activation status, and cytokine production; and 4) gene expression profiles will be used in such assessments. In addition, tumor biopsies will be collected and measures of tumor-based markers of: 1) intra-tumoral immune cells and immune-regulatory factors, and 2) gene expression in tumors will be analyzed to assess associations with antitumor activity.

An assessment of the effect of tocilizumab in combination with ipilimumab and nivolumab on biomarkers in peripheral blood, urine and tumor tissue (when collected) will be performed. Blood samples will be collected for analysis of immunoregulatory markers including, but not limited to, absolute lymphocyte count counts, natural killer (NK) cells and T-cell subtypes (CD4, CD8, Tregs), T cell intracellular cytokines (IFN-gamma, tumor necrosis factor [TNF]-alpha, IL-10, and IL-6), and serum as well as urine cytokine levels (IL-10, IFN-gamma, TNF-alpha). Absolute leukocyte counts will be evaluated in all patients on study. Flow cytometry will be performed for CD4 and CD8 T-cell expression of inducible T-cell co-stimulator gene (ICOS), Ki67, and eomesodermin gene (EOMES) as predictive markers (Wang W et al 2012). Given the positive correlation between sustained acetylation of the EOMES promoter and increased expression of this important T-cell transcriptional

regulator and findings that clinical benefit with ipilimumab is associated with pretreatment expression of EOMES in T cells, we will determine whether tocilizumab would increase EOMES promoter acetylation in T cells and potentially augment the clinical efficacy of ipilimumab and/or nivolumab. Multiplex analysis will be performed for serum and urine cytokines including IL-6, IL-10, and IFN-γ. Flow cytometry analysis of intracellular cytokines will be performed, all as pharmacodynamic markers of the effects of tocilizumab on immune cells. Exploratory analysis of mRNA expression in T cells (as assessed by gene expression profiling by Affymetrix and/or by quantitative real-time polymerase chain reaction [qRT-PCR]) may also be considered based on sample availability. Blood samples will be collected prior to the designated tocilizumab and/or ipilimumab with/without nivolumab dosing for the day of sample collection. As indicated above, there is particular interest in EOMES acetylation and expression in T cells, serum cytokine assays by multiplex analysis, and intracellular cytokine staining by flow cytometry for IFN gamma, IL-6, and IL-10, based on preclinical work with IL-6 receptor blockade.

In addition, pretreatment and on-treatment fresh tumor biopsies will be collected from up to 15 patients and examined for biomarkers including, but not limited to, T-cell markers such as CD4, CD8, CD45, and FOXP3, and activation markers such as granzyme B by IHC. Exploratory analysis of mRNA expression (as assessed by gene expression profiling by Affymetrix or by qRT-PCR) may also be considered based on sample availability. On-treatment biopsies will be collected during the induction cycle 1 between Days 35 and 42. On-treatment biopsies will be collected prior to administration of any scheduled morning dose of study therapy. The biopsy specimens will be split into two, and one half will be frozen, and the other half placed in formalin for paraffin imbedding. Two passes of a core biopsy needle may be taken if required for sufficient material.

7.9 Tissue Specimens

Pretreatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 15 unstained slides will be submitted for PD-L1 and other IHC assessments to NYU from NYU, The Angeles Clinic or Dana-Farber Cancer Institute's Pathology Laboratories prior to the patient's first dose of study drug. A minimum of 15 slides is ideal, but fewer slides based on substrate availability may be acceptable. In these situations, it is recommended to consult with the protocol team to discuss the specifics of the case.

Programmed death ligand-1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor and immune cells if a minimum of 100 evaluable tumor cells are present. Patients with tumor samples containing less than 100 tumors cells per tissue section will not be enrolled, but patients with positive, negative, or indeterminate (membrane staining is obscured by high cytoplasmic staining or melanin content) PD-L1 expression will be stratified based on their expression. In addition, this pretreatment tumor sample may be used to assess other putative predictive biomarkers of nivolumab with ipilimumab efficacy and/or to better characterize the tumor-immune microenvironment postresection. Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, ipilimumab, and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to, PD-1, PD-L2, TILs, or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. These pretreatment tumor samples may also be used

to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab and/or ipilimumab, including, but not limited to, other T cell checkpoint receptors and ligands (e.g., Lag-3, Tim-3) intratumoral immune cell subsets, including macrophages, NK cells, and B cells.

Optional tumor tissue samples may also be collected upon recurrence. This sample may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (e.g., Lag-3, Tim-3) and intratumoral immune cell subsets, including, but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab or ipilimumab the expression of potentially relevant predictive and/or prognostic melanoma biomarkers, including, but not limited to, BRAF mutation and PD-L1. Both the pretreatment tumor sample and the sample collected upon recurrence may be retrospectively assessed for BRAF mutation status, N-RAS mutation status, as well as for the expression of other immune or melanoma related genes, RNAs and/or proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization.

Upon occurrence of a ≥ Grade 3 drug-related AE and/or any lab abnormality regarded as a drug-related SAE, a biopsy of the affected organ(s) may be optionally collected. These samples may be used for the assessment of immune cell markers, including, but not limited to T cell, T regulatory cell and NK cell markers, as well as for the expression of MHC class I/II molecules.

7.10 Exploratory Serum and Urine Biomarkers

Blood samples for exploratory serum, plasma and urine biomarker analyses will be drawn at the specified time points indicated in Table 2. Additionally, serum samples will be collected when clinically safe and feasible, upon occurrence of a ≥ Grade 3 drug-related AE and/or any lab abnormality regarded as a drug-related SAE. Separate blood samples will be collected and processed for serum and plasma and then put in frozen storage. Urine samples will be frozen after collection. Serum, plasma and urine samples may be assessed by ELISA, seromics, microRNA profiling, circulating tumor DNA measurements, metabolomics, and/or other relevant multiplex-based protein assay methods for immune or melanoma-related factors that will predict for nivolumab or ipilimumab benefit or correlate with nivolumab or ipilimumab-related AEs. Numerous potential serum/plasma-based biomarkers are currently under investigation for their potential to predict or correlate with safety or efficacy to nivolumab, ipilimumab or other immunotherapies, including but not limited to levels of CRP, IL-6, soluble PD-L1, antitumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (e.g., soluble MICA), circulating tumor DNA, and microRNAs (such as, but not limited to, miR-513 and miR19b).

Samples will be stored for up to 10 years at NYU Langone Health at the following location:

522 First Avenue Room 1310 Smilow Building

New York, New York, 10016

The samples will only be stored for research related to this study and will be stored only using the subject number. No names or other subject identifiers will be used; a unique code

will be applied to the samples at the site. The linking key will be held by NYU. The genetic testing is related only to the subject's cancer and the potential use of tocilziumab as treatment and will not be used to predict an individual's risk for developing a disease or passing it to their children. The results of this testing will not be shared with the subjects.

7.11 Peripheral Blood Mononuclear Cells (PBMCs)

Peripheral blood samples will be taken prior to initiation of study therapy and at designated time points on-treatment (see Table 2 for additional details on the blood sample collection schedule) for PBMC preparation, except for sites where the stability of the samples after shipment to the Central lab cannot be guaranteed. Samples must be shipped within 48 hours to a designated central laboratory for processing.

These PBMC samples may be used for immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen specific T cell proliferation or activation pending emerging information from other nivolumab or ipilimumab studies.

7.12 Safety Endpoints and Assessments

Patients will be evaluated for safety if they have received any study drug.

7.12.1 Safety Reviews

All available clinical and laboratory data, and the nature, time of onset, and time to resolution of DLTs observed during dose escalation will be reviewed to determine whether an alternate dose schedule should be examined after consultation between the Investigators and BMS, if needed. If agreed upon, the alternate schedule will be identified by a protocol amendment and the MTD determined for the revised dose schedule. The dose escalation decision for Tocilizumab will be determined by an assessment of whether the addition of tocilizumab has potentially increased the toxicity associated with ipilimumab and nivolumab or potentially decreased the response rate of the regimen.

The data will be reviewed by a safety review committee consisting of the NYU Perlmutter Cancer Center DSMC, which will also review all safety data, specifically to review all Grade 3 or greater irAEs.

7.12.2 Dose-limiting Toxicities

The following AEs, if assessed to be possibly, probably or definitely related to tocilizumab, will be considered to be DLTs at CTCAE 5.0 (ref):

Hematologic Toxicity:

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) lasting > 7 days. If neutropenia is attributed to tocilizumab, ANC is to be repeated on Day 6 to determine if this is a DLT.

- Febrile neutropenia (ANC < 1,000/μL with a single temperature > 38.3°C [101.0°F] or 38.0°C [100.4°F] for > 1 hour).

- Grade 4 thrombocytopenia (platelet count < 25,000/μL).

- Grade 3 thrombocytopenia (platelet count 25,000/μL to 50,000/μL) with clinically important bleeding.

Non-hematologic Toxicity:

All other Grade 3 or Grade 4 non-hematologic toxicities may be due to immune therapy or tocilizumab, so etiology cannot be possible to ascribe to tocilizumab

Immune-related Toxicity:

All other Grade 3 or Grade 4 immune-related toxicities will be considered as potential DLTs. Immune-related toxicities among patients treated with nivolumab and/or ipilimumab have clustered among skin, gastrointestinal, endocrine and liver-related events as follows:

- Skin: alopecia, dry skin, hyperhidrosis, night sweats, pruritus, rash/desquamation, toxic epidermal necrolysis, urticaria, vitiligo.

- Gastrointestinal: abdominal discomfort or pain, anal ulcer, colitis (including ulcerative, hemorrhagic, ischemic, and megacolon), constipation, cramping, diarrhea (including hemorrhagic), diverticulitis/diverticulum, duodenitis, dyspepsia, dysphagia, enteritis, esophagitis, gastritis (including erosive), gastrointestinal hemorrhage (including rectal), hematochezia, ileitis, ileus, intestinal obstruction, intestinal perforation (including small and large intestines), melena, nausea, pancreatitis, peritonitis, stomatitis (including aphthous), vomiting, vasculitis gastrointestinal.

- Endocrine: adrenal insufficiency (including Addison disease), glucose tolerance impaired, hyperthyroidism hypogonadism, hypophysitis/hypopituitarism (autoimmune), hypothyroidism, pituitary enlargement, thyroiditis (autoimmune).

- Liver: hepatitis, jaundice.

Other treatment-related asymptomatic Grade 3 and Grade 4 laboratory investigations, excluding cardiac function tests, may be evaluated to determine whether dose cohorts should be expanded.

DLT will also include all immune-mediated adverse reactions (IMARs) that require withholding or discontinuation of at least one of the study drugs (tocilizumab, ipilimumab, nivolumab) per its label.

7.12.3 Dose-Delay Criteria

Because of the potential for clinically meaningful nivolumab and/or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories.

Dose delay criteria apply for all drug-related AEs (regardless of whether or not the event is attributed to ipilimumab and/or nivolumab). All study drugs, including ipilimumab and/or nivolumab and/or tocilizumab, must be delayed until treatment can resume.

Ipilimumab and/or nivolumab administration should be delayed for the following:

Any Grade 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 2 skin, drug-related AE.

Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade 3 lymphopenia or leukopenia does not require dose delay.
- If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Principal Investigator should be consulted for Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Patients who require delay of ipilimumab and/or nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume ipilimumab and/or nivolumab dosing when retreatment criteria are met.

7.12.4 Criteria to Resume Ipilimumab and/or Nivolumab Treatment After a Delay

Patients may resume treatment with study drugs when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if the Principal Investigator allows it.
- Patients may resume treatment when steroids are at 10 mg/day of prednisone or its equivalent or less.

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the patient must be permanently discontinued from study therapy, except as specified in discontinuation section.

7.12.5 Dose Omission Criteria for Nivolumab and Ipilimumab

Doses of ipilimumab and/or nivolumab should be omitted (not delayed) if any of the following criteria are met:

- Any Grade 3 nonskin, drug-related AE.
- Any Grade 3 skin, drug-related AE.
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
    - Grade 3 lymphopenia or leukopenia does not require dose omission.
    - If a patient has baseline AST, ALT, or total bilirubin that is within normal limits, omit dosing for drug-related Grade ≥ 2 toxicity.
    - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, omit dosing for drug-related Grade ≥ 3 toxicity.
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose omission.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants omitting the dose of study medication.

If the criteria to resume treatment (specified in Section 7.12.5.2) are met within the dosing window (Day 1, Week X ± 3 days), then the dose may be given.

Note: the term “interruption” is reserved for interruption of the actual IV infusion during administration. The terms omission and interruption should not be used synonymously when completing the case report form (CRF).

7.12.5.1 Adverse Event Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist Investigators in assessing and managing the

following groups of AEs: gastrointestinal, renal, pulmonary, hepatic, endocrinopathies, skin, and neurological. The management algorithms can be found in the nivolumab package insert.

While the ipilimumab IB contains management algorithms for similar AEs, it is recommended to follow the AE management algorithms for I-O agents in the nivolumab package insert.

For patients expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the nivolumab package insert.

Immune-related adverse events (irAEs) are specific events occurring within 100 days of the last dose (which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]), regardless of causality, for which patients received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for irAEs is endocrine events (e.g., hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

7.12.5.2 Criteria to Resume Treatment

Patients may resume treatment with any of the 3 study drugs when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose omissions for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR Grade 2 total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, colitis, uveitis or neurological toxicity, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if the treatment is withheld past the window period of the next scheduled time point per protocol to ensure adequate recovery from the AE or tapering of immunosuppression, the dosing should continue to be withheld until the subsequent scheduled time point.

If treatment is withheld > 6 weeks from the last dose, the patient must be permanently discontinued from study therapy, except as specified in Section 712.4.

7.12.6 Dose Modifications

Dose reductions or dose escalations of ipilimumab or nivolumab for individual patients are not permitted.

7.12.7 Treatment of Tocilizumab, Nivolumab or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, and tocilizumab is humanized, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE [version 5.0]) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional tocilizumab, nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the tocilizumab, nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the ipilimumab and/or nivolumab infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur then no further tocilizumab, nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used. If a patient has symptoms of anaphylaxis or hypersensitivity, or requires an interruption of tocilizumab because of symptoms of anaphylaxis or hypersensitivity felt due to tocilizumab, administration of tocilizumab must be discontinued permanently.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of tocilizumab, nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the patient as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous or intramuscular administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Tocilizumab, nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, corticosteroids).

7.12.8 Discontinuation Criteria

Treatment with ipilimumab and nivolumab should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 3 weeks OR requires systemic treatment.
- Any Grade 3 nonskin, drug-related AE lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 8 × ULN
            - Total bilirubin > 5 × ULN
            - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Creatinine greater than 6 × ULN.

- Any severe or Grade 3 immune-mediated adverse reaction that recurs on reintroduction of nivolumab with ipilimumab, or nivolumab alone, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Persistent Grade 2 or 3 immune-mediated adverse drug reactions that do not recover to Grade 1 or resolve within 12 weeks after the last dose of study drug.
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Dosing that is withheld > 6 weeks from the last dose with the following exceptions:
    - Dosing omissions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a patient with a dosing omission period lasting > 6 weeks from the last dose, the BMS Medical Monitor must be consulted.
    - Dosing omissions > 6 weeks from the last dose that occur for nondrug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a patient with a dosing omission period lasting > 6 weeks from the last dose, the BMS Medical Monitor must be consulted.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab or ipilimumab dosing.
- Tumor surveillance assessments and biomarker sampling should continue as per protocol even if dosing is omitted, and should be delayed for delayed dosing.

7.12.9 Treatment of tocilizumab-Related Toxicities

Non-hematological toxicities ≥ Grade 3 and considered to be treatment-related should be managed with tocilizumab treatment interruption until resolution of toxicity to ≤ Grade 1 or to baseline value. If the toxicity is adequately managed by routine supportive care (such as anti-emetics, anti-diarrheals, or electrolyte supplementation), treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose (Table 1). Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 6 : Tocilizumab Dose Modifications – Non-Hematological Drug-Related Toxicities Including Hepatotoxicity

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant hepatotoxic medications For persistent increases in this range, reduce tocilizumab dose to 2 mg/kg or interrupt tocilizumab until ALT/AST have normalized
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue tocilizumab
> 5x ULN	Discontinue tocilizumab

Patients withdrawn from tocilizumab treatment due to elevated liver function tests should have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to baseline within 6 months (or sooner, if deemed necessary by the sponsor or designee), an ultrasound and/or liver biopsy should be considered

7.12.10 Management of Tocilizumab in Event of Hematological Toxicities

Hematological toxicities ≥ Grade 3 and considered to be treatment-related should be managed with treatment interruption until resolution as described in Table 3. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt tocilizumab dosing. When ANC increases to > 1000, resume tocilizumab
< 500	Discontinue tocilizumab.

Patients withdrawn from tocilizumab treatment due to a reduced neutrophil count should be monitored for signs of infection, with treatment as deemed appropriate by the sponsor or designee, and should have a repeat white blood cell count with differential performed weekly until the ANC is above 1000 cells/mm^3 (1.0 x 10^9/L). If the ANC does not return to above 1000 cells/mm^3 (1.0 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or designee), a hematology referral is recommended.

Platelet count (cells/mm^3)	Action
> 100,000	Maintain dose.
50,000 – 100,000	Interrupt tocilizumab dosing. When platelet count increases to > 100,000, resume tocilizumab at 4 mg/kg
< 50,000	Discontinue tocilizumab.

Patients withdrawn from tocilizumab treatment due to a reduced platelet count should have a repeat platelet count performed weekly until the count is above 100,000 cells/mm^3 (100 x 10^9/L). If the platelets do not return to above 100,000 cells/mm^3 (100 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or designee), a hematology referral is recommended

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation patient administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

The start and stop time of the study drug infusions should be documented. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate nonserious AE or SAE page.

Adverse events will be categorized using the most current version of Medical Dictionary of Regulatory Activities (MedDRA). Adverse events and laboratory values will be graded according to the NCI CTCAE version 5.0. Baseline signs and symptoms are those that are assessed within 14 days prior to the first dose of study drug. Immune-related adverse events among treated patients will be specifically assessed as well.

8.2 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (defined as an event in which the patient 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 patient or may require intervention [e.g., 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. Potential drug-induced liver injury (DILI) is also considered an important medical event. See Section 8.10 the definition of potential DILI.

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.4.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 8.5 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery, planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

8.3 Nonserious Adverse Events

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

8.3.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin when patients give written informed consent to participate **and continue until 100 days from the last dose of study drug**. 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 patients.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 8.5). Follow-up is also required for nonserious AEs that cause withholding or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the electronic CRF .

8.4 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an AE
- Any laboratory test result abnormality that required the patient to have study drug omitted or discontinued
- Any laboratory test result abnormality that required the patient to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

8.4.1 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the sponsor, NYU, which will have the responsibility to report this event to BMS Worldwide Safety and Genentech Inc. and complete and forward a Pregnancy Surveillance Form to BMS and Genentech Inc.within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 8.5.

In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for patient safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with NYU DSMC, the pregnant patient may continue study drug after a thorough discussion of benefits and risk with the patient

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS and Genentech Inc..

In order to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

8.5 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 24 hours of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see definitions, sections 8.1, 8.2)

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

For studies involving collection of survival data/ follow up until progression free period/ Extended follow up period (select applicable) the investigator after the end of the adverse event reporting period (defined as {xx- days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.
Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via NYU emailing Genentech a Quarterly line-listing documenting single case reports sent by NYU to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the ‘Activation Package’.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by NYU to Genentech within five (5) calendar days from request by Genentech Inc.

the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech Inc

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The {Study Drug} Events of Special Interest are:
Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
- Treatment-emergent ALT or AST > 3 X ULN in combination with total bilirubin □ 2 □ ULN
- Treatment-emergent ALT or AST > 3 X ULN in combination with clinical jaundice

Exchange OF SINGLE CASE REPORTS

NYU will be responsible for collecting all protocol-defined Adverse Events (AEs) and Special Situation Reports (including pregnancy reports) originating from the Study for the Product.

Investigators must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs) and Special Situation Reports (including pregnancy reports) adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

8.6 Investigator reporting: notifying the study sponsor and Perlmutter Cancer Center Clinical Trials Office

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,

Serious adverse events, regardless of whether they are unexpected. The study sponsor will then report all medical events to BMS and Genentech Inc. directly.

All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to:

NYUPCCsafetyreports@nyulangone.org

AND

Jeffrey S. Weber, MD, PhD
Laura and Isaac Perlmutter Cancer Center
160 E. 34th Street
New York, NY 10016
Tel: 212-263-9333
Email: Jeffrey.Weber@nyulangone.org

AND

PCC Assigned Medical Monitor

Genentech Inc. at FAX (650) 225-4682 or (650) 225-4630

Follow-up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include any other diagnostic information that will assist in the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

8.7 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafetyreports@nyulangone.org

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.8 Sponsor reporting: Notifying BMS

All SAEs (whether related or not to study drug) and medically important conditions must be reported to BMS Worldwide Safety via fax or email within 24 hours/1 business day of becoming aware of the event. SAEs including pregnancies are to be reported using FDA MedWatch 3500.

Global Pharmacovigilance & Epidemiology (GPV&E)
Bristol-Myers Squibb Company

SAE Emailing Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: BMS: 1-609-818-3804

Genentech Inc. (650) 225-4682 or (650) 225-4630

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.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:
· Related: There is a reasonable causal relationship between study drug administration and the AE.
· Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

The Sponsor Investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

In addition to the Sponsor Investigator's responsibility to report events to their local HA, 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).

In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

Other important findings which may be reported by BMS as an Expedited Safety Report (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 (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS 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 IB. 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.

Following the patient's or the legal representative's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The Investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the Investigator believes that an SAE is not related to study drug, 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 Report Form.

All SAEs should be followed to resolution or stabilization.

8.8.1 NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the time of signing of informed consent and is intended to establish a baseline status for the subjects.

8.8.1.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at the time of signing of informed consent. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.9 Sponsor reporting: Notifying Genentech

8.9.1 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the tocilizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the tocilizumab, and the AE cannot be readily explained by the subject’s clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the tocilizumab; and/or the AE abates or resolves upon discontinuation of the tocilizumab or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the tocilizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to tocilizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

8.9.2 AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The *tocilizumab* Events of Special Interest are:
Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law noted below. The risk of serious hepatotoxicity associated with the use of tocilizumab was also recently described in a "Dear Investigator Letter" distributed by F. Hoffmann-La Roche Ltd:
    - **Serious or medically significant hepatic events**
    - **Serious and/or medically significant infections**
    - **Myocardial infarction/Acute coronary syndrome**
    - **Gastrointestinal perforations**
    - **Malignancies**
    - **Anaphylaxis/Hypersensitvity reactions**
    - **Demyelinating disorders**
    - **Stroke**
    - **Serious and/or medically significant bleeding events**

8.9.3 Exchange OF SINGLE CASE REPORTS

Perlmutter Cancer Center will be responsible for collecting all protocol-defined Adverse Events (AEs) and Special Situation Reports (including pregnancy reports) and product complaint (with or without AEs) originating from the Study for the Product.

Investigators must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs) and Special Situation Reports (including pregnancy reports) adequately to Genentech within the timelines described below.

The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.
These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on a NYU CTO Medical Events Form to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. See section 8.9.2 for AESIs

- **Special Situation Reports**

Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports**
In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - Drug interaction
  - Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)
  - Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

It is understood and agreed that the Sponsor will perform adequate due diligence with regard to obtaining follow-up information on incomplete AE, Special Situations and pregnancy reports.

8.9.4 Post-Study Adverse Events

For studies involving collection of Extended follow up period the investigator after the end of the adverse event reporting period (defined as {5 years after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.
Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

8.9.5 Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Perlmutter Cancer Center, emailing Genentech a Quarterly line-listing documenting single case reports sent Perlmutter Cancer Center, to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Perlmutter Cancer Center, to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

8.9.6 Aggregate Reports

IND Annual Reports

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

8.9.7 Other Reports

Perlmutter Cancer Center, will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

8.9.8 Study Close Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

E-mail: ACTEMRA IST Central Mailbox: actemra-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

8.9.9 Queries

Queries related to the Study will be answered by Perlmutter Cancer Center. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. Perlmutter Cancer Center agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

8.9.10 Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.
The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. Perlmutter Cancer Center agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

8.10 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 8.5 for reporting details).

8.11 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.5 for reporting details).

Potential DILI is defined as:

Aminotransaminase (ALT or AST) elevation > 3 × ULN

AND

Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of aminotransaminases elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.12 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study Investigator as per standard medical/clinical judgment.

Appropriateness of Measurements

The efficacy and safety assessments planned for this study are recognized as reliable, accurate, and relevant to the disease condition and considered appropriate for this clinical study. Tumor assessments will be performed objectively using CT or MRI to measure lesions. Assessment of disease progression using ECOG performance status and irRC is accepted standard.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

9.1 Data Monitoring Committee and Other External Committees

The Data Safety Monitoring Committee (DSMC) at the Laura and Isaac Perlmutter Cancer Center of NYU-Langone Health will provide oversight of safety and efficacy considerations in this protocol. Additionally, the DSMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of patients enrolled in the study. The DSMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and ipilimumab with tocilizumab. The DSMC will act in an advisory capacity and will monitor patient safety and evaluate the available efficacy data for the study. When required, adjudicated events will be submitted to the DSMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation and schedule.

The DSMC will have access to periodic reports of safety and efficacy to allow a risk/benefit assessment. The NCI approved DSMC charter is available online at https://central.nyumc.org/clin/cancer/NYUR/_layouts/15/WopiFrame.aspx?sourcedoc=/clin/cancer/NYUR/Shared%20Documents/Standard%20Operating%20Procedures/DSMC%20SOP.pdf&action=default This committee meets monthly.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this pilot trial will be monitored by DSMC *quarterly* (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: patient listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications, adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a recommendation is made if further action is required, the Investigator must respond within the time period designated by the DSMC.

10 STATISTICAL METHODS

10.1 Sample Size Considerations

The first 12 patients at the initial dose level will be evaluated for DLTs. Unacceptable toxicity will be defined by a DLT rate of ≥50%. If we observe ≥6 DLTs in these first 12 patients, we reject the null hypothesis that the DLT rate is <50% (one sided α=0.05, power=80%). If we do not reject the null hypothesis, the current dosing continues with 6 additional patients up to 18 patients (which count as the first stage of the optimal 2-stage Simon design). There will be no adjustment to the operating characteristics of the optimal 2-stage Simon design.

To evaluate the co-primary endpoint of the rate of grades 3-5 treatment related immune-related adverse events, a two-stage Simon Optimal design will be used. With 67 patients in two stages (Stage 1: 12+6 patients, Stage 2: 49 patients) we can detect a reduction in the rate of the primary toxicity endpoint from 35% to 20% in grades 3-5 treatment related irAEs, with alpha of 0.05 and power of 80%.

With the planned 67 patients for the co-primary toxicity evaluation of immune-related adverse events, we can simultaneously evaluate the co-primary efficacy endpoint evaluated by overall response rate (ORR) at 6 months over the 18 months of treatment. Using a Simon 2-stage optimal and minimax design, we can test the null hypothesis that the ORR rate at 24 weeks is less than or equal to 50% versus the alternative that it is 70% or greater with a maximum of 67 patients with alpha of 0.045 and power of 0.85.

The evaluation of stage 1 will occur when the first 18 patients could have been observed for the 6-month period following entry. If 6 or more of the first 18 patients in stage 1 experience a grade 3-5 treatment related immune-related adverse event, the rate of toxicity would be considered unacceptable (grade 3-5 irAE rate≥35%)

If fewer than 6 patients experience a treatment related immune-related adverse event, the rate of toxicity would be considered acceptable (irAE≤20%) .

With an evaluation of the first 18 patients entered on study (who would complete the study before the end of study year 2) in stage 1, if we observe 10 or fewer responses, the response rate would be considered unacceptable (ORR≤50%) . Otherwise, if we observe more than 10 responses, the response rate would be considered acceptable (ORR≥70%

If both toxicity rate and efficacy rate are acceptable, - continue to complete stage 2 with up to 67 patients.

If toxicity rate is acceptable and response rate is unacceptable , – increase dose to level 2 (tocilizumab 6 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients.

If toxicity rate is unacceptable (due to irAE rate of grades 3-5 >=35% felt due to tocilizumab), and response rate is acceptable, – decrease dose level to -1(tocilizumab 2 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients.

If toxicity rate is unacceptable (due to irAE rate of grades 3-5 >=35% felt due to

IPI and/or NIVO), and response rate is acceptable, – increase dose level to 2(tocilizumab 6 mg/kg every 6 weeks) and restart DLT evaluation with 12 patients.

If both toxicity rate and response rate are unacceptable – stop early and consult with IRB and/or FDA.

At the end of Stage 2, if there are 39 or fewer responses out of the total of 67 patients, the regimen would be considered unsuccessful. Similarly, if at the end of stage 2, there are 19 or more treatment related grade 3-5 irAEs, the trial would be considered unsuccessful to have met its objective of reducing the toxicity rate to 20% or less.

There is no adjustment for these simultaneous assessments of efficacy and safety.

Accrual will occur over 1.5 years, 22-23 patients per institution or 14 patients/year/institution. .

Enrolled Population: All patients who sign an ICF and are registered into the trial.

As-Treated Population (ATP): All patients who receive any study drug of nivolumab, ipilimumab, or tocilizumab.

DLT Evaluation Population: All patients who receive any study drug of nivolumab, ipilimumab, or tocilizumab and either experience a DLT during the first cycle or complete the first cycly without experiencing a DLT. Patients who do not complete the DLT period for reasons other than toxicity will be replaced.

Biomarker Population: All patients in the ATP who have available biomarker data (PD-L1 expression status and other assays).

10.2 Analysis Schedule

10.2.1 Interim Analysis

Interim assessment of the two co-primary endpoints will occur as described in the sample size considerations section.

10.2.2 Final Analysis

An analysis of the co-primary endpoints is planned after the last patient completes the maintenance phase at the end of one year of treatment or discontinues from the study.

10.3 Statistical Methods

10.3.1 General Methods

Statistical analyses will be primarily descriptive in nature, since the goals of the Phase II study is to evaluate the toxicity and efficacy of tocilizumab in combination with nivolumab and ipilimumab.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized

showing the number and percentage (n, %) of patients within each classification. Graphical displays will be provided where useful in the interpretation of results.

10.3.2 Disposition of Patients

Patients who are screened for study entry and do not meet the eligibility criteria will be listed only. The number and percentage of patients in each population and discontinued early, along with the primary reasons for early discontinuation, will be tabulated by study stage.

10.3.3 Demographics and Baseline Characteristics

Demographic data (gender, age [years], age group, race, ethnicity, height, weight, body mass index), baseline characteristics, and baseline disease characteristics for patients enrolled will be summarized by study stage.

10.3.4 Extent of Exposure

Study drug administration and information on dose reductions will be summarized for each dose level. Descriptive statistics for patients who started and completed each treatment cycle, including the number of doses missed/held, will be presented by treatment cycle and overall. Furthermore, descriptive statistics for the number of actual doses received and percentage of expected dose received will be summarized by treatment cycle. A tabular summary and listing of drug administration and dose intensity by treatment cycle, a by-patient listing of the dose date and time, and the dose amount administered will also be presented.

10.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the most current World Health Organization (WHO) Drug Dictionary. Prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that started up to 28 days before the first dose of study drug and stopped before the first dose of any study drug. Concomitant medications will be defined as medications documented on the Prior and Concomitant Medications eCRF that a patient started up to 28 days before the first dose of study drug or continued to take on or after the first dose of any study drug. Prior and concomitant medications will be summarized in separate tables, with concomitant medications coded using the WHO Drug Dictionary. All concomitant medications administered will be tabulated in a data listing. The statistical analysis plan (SAP) may include more details regarding how to summarize medications.

10.3.6 Safety Analysis

Safety data will be summarized when 12 patients have completed the second 42-day cycle during the induction phase. In addition, safety data will be summarized for the entire treated population at the termination of the study.

Safety evaluations will be based on the incidence, intensity, and type of AEs, and changes in the patient's physical examination findings, ECOG performance status, vital signs, oxygen saturation, ECG findings, and clinical laboratory results. Safety analysis will be performed in the ATP. Summarization will focus on occurrence rates of any SAEs; treatment-emergent

AEs by system organ class and preferred term; rate of discontinuation study treatment due to AE; or toxicity based on clinical laboratory assessment and rates of hematologic toxicity.

Adverse events will be coded using the MedDRA for purposes of summarization. All AEs occurring on study will be listed in by-patient data listings. Treatment-emergent AEs will be tabulated, where treatment emergent is defined as any AE that occurs after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered drug-related by the Investigator.

Adverse events that are considered related to treatment (possibly or probably drug related) will also be tabulated; it should be noted, however, that without a control the primary safety conclusions must be based on overall incidence rates and not those considered treatment-related. The treatment-emergent AEs will also be summarized by system organ class, preferred term, and maximum severity.

A separate listing and summary of all irAEs and inflammatory events regardless of causality (IERC) will be provided. In addition, the irAE rate will be estimated and a 95% confidence interval will be constructed for the overall all grade irAE and the Grade 3-4 irAE rate, based on the Clopper-Pearson method.

Deaths and AEs resulting in study discontinuation will be tabulated.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Shift tables will be produced for selected laboratory parameters, to include hemoglobin, WBC count, ANC, absolute lymphocyte count, platelet count, AST, ALT, bilirubin, creatinine, alkaline phosphatase, and electrolytes. These tables will summarize the number of patients with each baseline NCI CTCAE grade and changes to the maximum NCI CTCAE grade.

Changes in vital sign parameters (including blood pressure, heart rate, and temperature) will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated. Change in ECOG and oxygen saturation at each visit will be tabulated.

Any significant physical examination findings will be listed.

ECG findings will be presented in data listing format. Abnormalities of ECG, QT interval, and QTc interval by Bazett’s and Fridericia’s formulas will be summarized.

Additional safety analyses may be determined at any time without prejudice in order to clearly enumerate rates of toxicities and to define further the safety profile of study drug.

10.3.7 Efficacy Analysis

All patients entered into this Phase II trial will be evaluated for efficacy. Patients will be stratified by safety cohort (if applicable) and by stage in the two-stage design summaries. Efficacy analysis will be performed on the as treated population. The analysis will be based

on the change from baseline in tumor measurements as assessed by imaging (CT scan or MRI) studies and the ORR by 6 months assessed according to RECIST version 1.1 criteria (Eisenhauer, E et al 2009), which is the primary efficacy criteria and irRC, which will be used to determine progression that mandates stopping therapy

The ORR will be the percentage of patients who achieve overall response of CR or PR at month 6. The immune-related response rate will be the percentage of patients who achieve the immune-related best overall response of irCR or irPR.

The number of patients who have at least SD or better per RECIST 1.1 will be included as the calculation of DCR.

Progression-free survival will be defined as the time from the first dose of study treatment to the first documentation of disease progression or death from any cause during the study using RECIST 1.1..

Time to progression will be defined as the time from first dose of study treatment to the first documentation of disease progression using RECIST 1.1.

For responders, time-to-tumor response and response duration will be summarized
Time-to-tumor response will be defined as the time from first dose of study treatment to the first documentation of response (either PR or CR).

Duration of response will be defined as the time from the first PR or CR to the first documentation of disease progression using both RECIST and irRC.

Kaplan-Meier procedures will be used to characterize these time-to-event curves (PFS, time to progression, response duration) when there is censoring (the detailed censoring rules will be documented in the SAP); descriptive summary statistics will be provided for time to tumor response. The 95% confidence interval for ORR, DCR, and prolonged disease rate based on Clopper-Pearson method will be provided.

10.3.8 Pharmacodynamics Biomarker Analysis

Biomarker analysis will be performed on the Biomarker population. The biomarker endpoints will be summarized descriptively as appropriate.

The following blood inflammatory proteins/cytokines will be assessed at baseline, week 7 and 37:

Inflammatory cytokines: IL-1β; IL-6; IL-8, IL-10, IL-12, TNF-alpha and gamma interferon
Acute phase reactants: C reactive protein, Serum amyloid A, Serum amyloid P, Haptoglobin and Mannose binding protein, alpha-1 anti-trypsin
Complement components: C5a, C3a, C3b, C1q, C1r, complement factor B and C9

Selected urine biomarkers will be measured at baseline, week 7 and 37: IL-1β; IL-6; IL-8, IL-10, IL-12, TNF-alpha and gamma interferon

Statistical summary: The utility of an inflammatory protein signature will be assessed using a scoring system based on positivity for each of the above elements. We will use penalized

regression methods to select predictors and adjust for potential confounders. We will test whether the signature predicts ORR as the primary clinical endpoint using logistic regression and PFS as secondary, using Cox models, respectively.
Expected results: We expect that baseline values and changes in inflammatory proteins from the above list, especially CRP, will distinguish patients who benefit from tocilizumab with combination checkpoint inhibition and that those with the highest levels of the inflammatory proteins and cytokines will benefit the most.

The following flow cytometric T cell phenotype studies will be performed, based on preliminary data presented herein and in the literature; they will be assessed at baseline, and at week 12:
T cell function: CD8+ and CD4+ Ki-67; CD8+ and CD4+/*STAT* 1, 3, 4 and 6; CD8+ and CD4+/pLck, pZAP70 and pERK; CD8+ and CD4+/IFN-gamma, TNF-alpha, granzyme B and IL-1β
Immune cell panels: T cell proliferation, checkpoint, activation, memory; MDSC (granulocytic/myeloid)
Statistical summary: Success would consist of defining a selected baseline signature that includes selected markers from those noted above associated with co-primary endpoints of grades 3-5 irAEs and ORR, and the secondary endpoint of PFS in the trial with a sensitivity of at least 0.90 and a specificity of 0.80 with FDR $\leq$ 0.01 using logistic and Cox regression models and adjusting for potential confounders. As a control group, we will use 40 specimens of PBMC from a phase II trial of second line PD-1 antibody to determine if biomarkers are checkpoint specific or determined by CRP depletion with IL-6 blockade.
Expected results: We expect that changes in T cell phenotypes and functional determinations will distinguish those patients who benefit from combination tocilizumab and checkpoint inhibition in this trial.

The following dendritic cell studies will be performed, based on preliminary data presented herein and the literature, at baseline and week 12:
Dendritic cell phenotype:
CD40, CD80, CD83, CD86, CD205, CD206, HLA-DR
Dendritic cell function:
Fluorescinated dextran uptake

Statistical summary: The utility of a signature composed of dendritic cell phenotypes and a functional determination will be assessed in the current study using similar approaches to those described above. We will test whether the signature predicts grades 3-5 irAE toxicity as the primary endpoint and ORR as well as PFS as the secondary clinical endpoints using logistic regression and PFS as secondary, using Cox proportional hazards models and adjusting for potential confounders as above.

Expected results: We expect that changes in some dendritic cell phenotypes and functional determinations will distinguish those patients who benefit from combination tocilizumab and ipilimumab/nivolumab checkpoint inhibition in this trial, assessed by a lower toxicity, higher response rate and longer progression-free survival.

We will merge the data from serum, T cell and dendritic cell assays into one comprehensive dataset so that each subject has a vector of measurements for multiple biomarkers, including high-dimensional mass spec protein data with repeated measurements. These biomarkers are measured on the same subjects, so we expect correlations and interactions among them for outcomes that are of biologic interest. One can exploit these interactions to develop a single comprehensive, integrated model. Such a comprehensive model can increase predictive accuracy by taking advantage of synergistic interactions between the multiple types of correlated biomarkers measured in the same patients above. Several approaches can be used to evaluate synergies and other interaction including network or pathway analyses in bioinformatics/machine learning and/or the formal assessment of interactions using statistical tests. Moreover, we can use regression models to evaluate how strongly the CRP signature predicts the phenotype of the T-cells or DCs. Further, we can use regression analysis for ORR and PFS to see how much the effect of inhibiting IL-6 by tocilizumab as captured by the CRP signature is modulated by the functional changes in T-cells or DCs in the patients in the tocilizumab + IPI + NIVO treatment arm with comparison to the 40 samples with the inhibition of PD-1 alone. We have expertise in identifying and characterizing interactions as well as in modeling and integrating heterogeneous and multi-scale medical data for patients' response, survival and for drug resistance. To build comprehensive predictive models we will use machine learning-based feature selection methods, including those described in Weber et al[12], to identify optimal low-dimensional subsets from candidate high-dimensional features that accurately predict ORR and PFS. In particular, approaches to dimensionality reduction include cluster analysis, penalized latent class regression models, random forest, and various machine learning techniques. We will also incorporate other baseline tumor-based predictors such as BRAF mutation status and PD-L1 express levels. We will decide whether they should be baseline predictors or as stratification factors. We will use random splitting into discovery and testing sets and use cross validation to identify predictive models and evaluating the models via averaging the performance in testing sets only as exploratory analyses.

High resolution flow cytometry including the new CITE-Seq technology will be performed on peripheral blood mononuclear cells harvested prior to treatment and at weeks 6 and 12 to aid in defining possible predictive pretreatment and pharmacodynamic markers. We will also assess tumor biopsies for infiltrating cells with biopsies pretreatment, and post treatment in selected patients.

The change between pre-dose and post-dose time points in the levels of analytes including CRP, IL-6 and other acute phase reactants will be determined in blood samples. A summary report will be generated with the pharmacodynamics analysis.

Procedures for Reporting Deviations to Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor, NYU Langone Health or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

Electronic CRFs will be prepared for all data collection fields. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For eCRFs, review and approval/signature is completed electronically. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance (QA) specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or Trial master. Relevant source documentation to be reviewed by the QA specialists throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11.3 Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The NYU Data Safety and Monitoring Committee (DSMC) will review the study quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events. In addition, the study may be evaluated by BMS and/or Genentech Inc.internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS and/or Genentech Inc.audit reports will be kept confidential.

The Investigator must notify BMS and Genentech Inc. promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF and is administered study drug.

In accordance with current Good Clinical Practice (cGCP) and The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The Investigator must permit the monitor, the IRB, the Sponsor's internal auditors, and representatives from regulatory authorities to have direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

11.3.1 Data Monitoring Committee

This investigator initiated and sponsored study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University Perlmutter Cancer Center. The DSMC operates based on the 2018 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the New York University Langone Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the director of the New York University Perlmutter Cancer Center (Benjamin Neel, MD/PhD). Per the New York University Perlmutter Cancer Center Institutional Data Safety and Monitoring Plan, this Phase II trial will be monitored by the DSMC at least every 6 months and as often as quarterly (from the date the first patient is enrolled), with outcome data presented upon completion of each cohort. DSMC will review the study whenever there is action to take in terms of dosing of tocilizumab. However, taking the appropriate action will not be contingent upon the DSMC review. This review includes accrual data, subject demographics, and adverse events. The Principal Investigator is required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months or sooner if indicated.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review, Phase I/II committee review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

1. Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data managers and research team.

2. DSMC, quarterly

3. IRB: An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data

4. In addition, the quality assurance unit, the quality assurance unit will monitor this trial every 4-6 weeks, this includes real- time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

11.4 Data Management and Coding

NYU's Datacore will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the Clinical Trials Office at NYU.

Study centers will enter data directly into an EDC system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be US Title 21 Code of Federal Regulations Part 11 compliant.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

11.5 Monitoring of Other Participating Institutions

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a Site Investigator and staff. If remote EMR access is not available, then the Site Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high-priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

12 RECORDS AND SUPPLIES

12.1 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of investigational product (inventoried and dispensed) is maintained at the study site. 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 identification number or batch number
- Amount dispensed to and returned by each patient, including unique patient identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (e.g., lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS and/or Genentech
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

12.2 Records Retention

The Investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS and/or Genentech Inc., whichever is longer. The Investigator must contact BMS prior to destroying any records associated with the study.

BMS and/or Genentech Inc. will notify the Investigator when the study records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to BMS and/or Genentech Inc.

12.3 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between BMS and the Sponsor.

13 ETHICS

13.1 Institutional Review Board/Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB/IEC together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB/IEC as required. On completion of the study, the IRB will be notified that the study has ended.

13.2 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB for review and approval/favorable opinion
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)) must be sent to BMS and Genentech Inc..

If an amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

If the revision is done via an administrative letter, Investigators must inform their IRB(s).

13.3 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

13.4 Ethical Conduct of the Study

The Investigators and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, cGCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.5 Informed Consent Process

13.5.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol Informed Consent.

13.5.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULH PCC CTO

13.5.3 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to cGCP.

The Investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the patient ICF will be provided to the patient or their authorized representative.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IRBs (and regulatory authorities, if required). The study patients will be informed about this new information and re-consent will be obtained.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies or the SOP of the local institution.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the stud, the patient will mark an X where his/her name would go and the witness will sign the consent form.

13.6 Subject Recruitment

Target enrollment for this study is 67 patients over 1.5 years. Patients will be recruited from physicians participating in this study. Consenting, screening, and treatment will take place at the NYULMC PCC, The Angeles Clinic in Los Angeles, Dana Farber Cancer Institute in Boston or participating sub-sites under supervision of the Site PIs. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility, see Section 4.2 and 4.3

3. Submit registration to NYU Langone Perlmutter Cancer Center CTO

4. Receive registration confirmation from the NYU Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows the established procedures of the NYULMC Perlmutter Cancer Center Clinical Trials Office.

13.6.1 Documentation of Consent

The Principal Investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

13.7 Registration Procedures

13.7.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form

2. Complete signed and dated eligibility checklist

3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of CTO receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number will be disbursed to the study team upon registration.

Upon receipt of ICF, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point at which the patient is considered accrued on study. If tissue is submitted prior to eligibility confirmation, a unique study number may also need to be issued.

13.7.2 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality

Assurance Unit will provide a remote extensive monitoring including real-time review of all eCRFs to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed within four weeks of enrollment. Decisions from the DSMB will be disseminated to other study sites during routine calls of the investigators at each site, which will occur monthly.

13.7.3 Patient Registrations at Other Participating Institutions

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office and an SIV is conducted, an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyulangone.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within the designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Weber. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to

the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Subjects must not start any protocol procedures prior to registration; each participating institution will order the study agent directly from the supplier, BMS, in the case of ipilimumab and nivolumab, and Genentech Inc. in the case of tocilizumab..

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, BMS, Genentech Inc. and Dr. Weber.

13.8 Patient Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, BMS. Genentech Inc., the IRBs approving this research, and the US FDA, as well as that of any other applicable agency (ies), will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patients' identities will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last patient), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator. Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

14.1 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Patient recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement governing [study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the clinical trial agreement.

15 REFERENCES

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16 APPENDICES

16.1 RECIST Version 1.1 Quick Reference

The following is a quick reference guide for the revised RECIST (version 1.1) guidelines with minor modifications.

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
    - Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
    - Measurable lesions - lesions that can be accurately measured in at least one dimension with longest ≥ 10 mm with CT scan or MRI. For lymph nodes, the short axis must be > 15 mm to be assessed as pathological.
    - Nonmeasurable lesions - all other lesions, including small lesions (longest diameter (LD) < 10 mm with CT scan or MRI), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.
- All measurements should be taken and recorded in metric notation, using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols. PET-CT with contrast may be used if the CT portion satisfies the criteria above.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. MRI is to be avoided for lung lesions.
- Since one of the secondary endpoints of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the ULN, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Nontarget" Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of Target Lesions

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

Abbreviation: LD = longest diameter

Evaluation of Nontarget Lesions

Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more nontarget lesions or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions[a]

[a] Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of Overall Response Rate

The ORR is the response recorded from the start of the treatment until month 6 (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

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

Confirmation

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

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at not less than 6 weeks) that is defined in the study protocol.

Duration of Overall Response

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

Duration of Stable Disease

- Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between 2 measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response Review

- Since response rate is one of the secondary endpoints, all responses will be reviewed locally by an expert. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of Results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) CR, 2) PR, 3) SD, 4) PD, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4 to 9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4 to 9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment

efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% CIs should be provided.

16.2 Appendix 2: Immune-related Response Criteria (irRC)

The following summary of assessment of disease response using irRC is from the Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria (Wolchok, 2009).[

The irRC, antitumor response is based on the total measurable tumor burden of index and measurable new lesions. Thus, each net percentage change in tumor burden represents the size and growth kinetics of both old and new lesions as they appear.

The baseline sum of the product of the diameters for all index lesions identified is the immune-related sum of products of diameters (irSPD). At each subsequent tumor assessment, the sum of products of diameters (SPD) of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden).

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at baseline).

Time Point Overall Response Using irRC

The overall assessment of immune-related response reported at each time point will be based on the following criteria (as defined in table that follows):

- **Immune-related complete response (irCR)**
  Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions

- **Immune-related partial response (irPR)**
  A decrease relative to baseline of the irSPD of 50% or greater

- **Immune-related stable disease (irSD)**
  An evaluable response that fails to meet criteria for irCR or irPR, in the absence of PD

- **Immune-related progressive disease (irPD)**
  At least a 25% increase in the irSPD (based on irSRSPD of all index lesions and any measurable new lesions) over the nadir irSPD

- **Immune-related unknown response (irUN)**
  Tumor assessments that cannot be evaluated (eg, because of image quality, inability to assess all relevant lesions, etc)

Patients will be able to continue treatment by irRC criteria even if there is progression of disease by RECIST 1.1 if the following conditions are met:

- Absence of clinical symptoms or signs indicating clinically significant progressive disease (PD)
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention
- Patients will be re-consented prior to continuation of therapy

Immune-Related Response Criteria Definitions

Index Lesions	Non-Index Lesions	New Lesions	% Change in Tumor Burden (Including New Lesions)	Overall irRC Response
CR	CR	Any	– 100%	irCR
CR	Any	Any	> –100% to ≤ –50%	irPR
			> –50% to < +25%	irSD
			≥ +25%	irPD
PR	Any	Any	> –100% to ≤ –50%	irPR
			> –50% to < +25%	irSD
			≥ +25%	irPD
SD	Any	Any	> –50% to < +25%	irSD
			≥ +25%	irPD
PD	Any	Any	≥ +25%	irPD
UN	Any	Any	UN	irUN

Abbreviations: CR = complete 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; irUN = immune-related unknown response; PD = progressive disease; PR = partial response; SD = stable disease; UN = unknown response.