THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

PHASE II STUDY OF ADJUVANT NIVOLUMAB IN PATIENTS WITH RESECTED STAGE IIB/IIC MELANOMA

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Columbia University research policies.

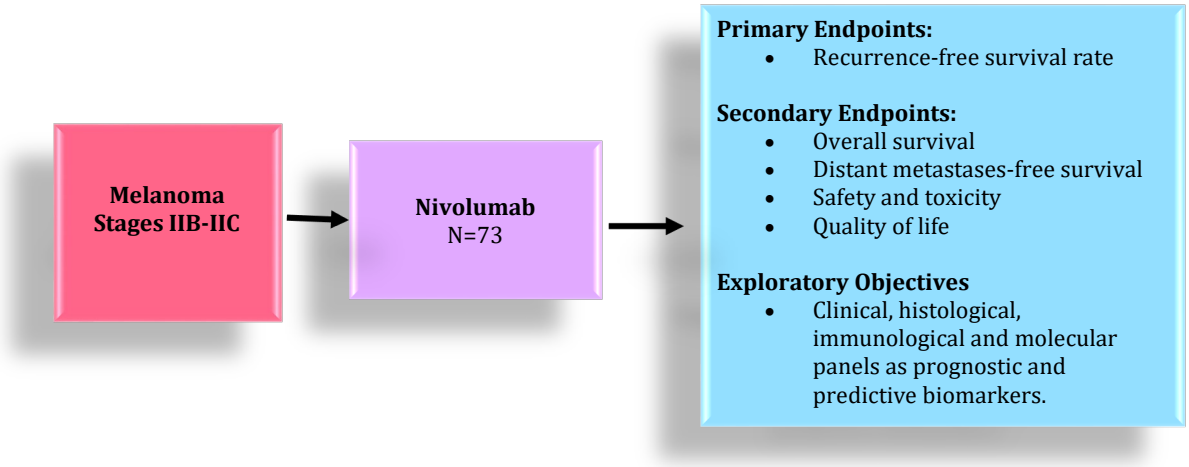
List of Abbreviations

AE	Adverse Event/Adverse Experience
AJCC	American Joint Committee on Cancer
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CT scan	Computer Axial Tomography scan
DFS	Disease-free survival
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFNa	Interferon-alfa
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
irRC	Immune related Response Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PD	Progressive Disease
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PO	By Mouth
PR	Partial Response
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
QoL	Quality of Life
RFS	Recurrence-free survival
SAE	Serious Adverse Event/Serious Adverse Experience
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SOP	Standard Operating Procedure
TNM Staging	Tumor, Node and Metastasis Staging
UAP	Unanticipated Problem

Protocol Synopsis

Protocol Title:	**Adjuvant Nivolumab in Patients with Resected Stage IIB/IIC Melanoma**
Site Number and Names:	Sidney Kimmel Cancer Center, Thomas Jefferson University Columbia University Medical Center Cancer Institute of New Jersey Fox Chase Cancer Center University of Pennsylvania
Research Hypothesis:	Nivolumab administered in the adjuvant setting will improve clinical outcomes in patients with resected American Joint Committee on Cancer stage IIB or IIC cutaneous melanoma (eighth edition.)
Study Schema: (Drugs/ Doses/ Length of Treatment)	We will enroll approximately 63 evaluable subjects with resected stage IIB or stage IIC cutaneous melanoma in this multicenter single arm phase II clinical trial. All eligible patients will receive 48 weeks of nivolumab 480 mg IV every four weeks for 48 weeks. Patients will be followed for disease recurrence and overall survival.
Study Objectives:	**Primary endpoint:** • Recurrence-free survival rate at 24 months. **Secondary endpoints:** • To evaluate and estimate the median duration of overall survival (OS) in Stage IIB-IIC melanoma patients. • To evaluate and estimate the median duration of distant metastases-free survival (DMFS) in Stage IIB-IIC melanoma patients. • To assess safety and toxicity using CTCAE V5.0 • To assess quality of life using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) quality of life instrument **Exploratory Objectives** • To assess and compare clinical, histological, immunological and molecular panels as prognostic and predictive biomarkers.
Study Type:	Multicenter single arm phase II clinical trial
Accrual Goal: (Total number of patients)	We will require enrollment of 63 evaluable patients. To account for a potential loss to follow up rate of 15%, our target total number of enrolled subjects is 73.
Accrual Rate:	We anticipate an accrual of 3-4 patients per month once all participating centers are activated.

Schematic of Study Design:



1. INTRODUCTION

1.1 Research Hypothesis

Newer immunotherapeutic agents such as nivolumab, though not without side effects, possess a better safety profile than ipilimumab and high dose IFN-alfa, with greater efficacy in the metastatic setting.[7,8] We theorize that adjuvant nivolumab therapy for melanoma patients with IIB-IIC disease may result in improved clinical outcome in this group of patients. Our hypothesis is that 48 weeks of adjuvant nivolumab in stage IIB-IIC cutaneous melanoma will improve the recurrence-free survival (RFS) rate at 24 months from 70% to 85% (50% improve in RFS.)

1.2. Rationale for the Proposed Study

1.2.1. Effective adjuvant treatment options are needed for patients with stage II melanoma

The American Joint Committee on Cancer (AJCC) staging system stratifies cutaneous melanoma patients into stages 0 through IV, with generally favorable prognoses for patients with AJCC stage I and stage II disease. Surgical excision is the treatment of choice for stage I and II melanoma and is curative in most cases; therefore, adjuvant therapy is not standardly recommended. Nevertheless, a subset of patients within early stage melanoma is at increased risk of recurrence and death from disease and more patients with stage I and stage II melanoma will die than those with more advanced disease at the time of diagnosis.[1,2]

The 5-year survival for stage IIA and stage IIB melanoma has previously been reported to be 80% and 70%, respectively.[1] Based upon more recent retrospective data of over 300 patients with stage IIB and stage IIC melanoma from Thomas Jefferson University, the University of North Carolina, and Memorial Sloan Kettering Cancer Center, the recurrence rate for stage IIB patients is approximately 32%. For patients with stage IIC disease, the recurrence rate is 46%[17,18] . Using these data sets, the rate of recurrence free survival at 24 months can be conservatively estimated at 70%.

1.2.2. The current and emerging adjuvant treatment landscape largely excludes patients with early stage melanoma

The majority of melanoma clinical trials conducted in the adjuvant setting have enrolled patients with melanoma at high risk for relapse, frequently defined as those with stage III disease by the AJCC staging criteria. While many adjuvant therapies have been examined, only two agents have been

shown to be of benefit. Interferon-alfa (IFNa) was shown to prolong disease-free (DFS) and improve overall survival (OS) in a small subset of patients.[3] More recently, ipilimumab, the anti-CTLA4 antibody, has been shown to significantly decrease the rate of recurrence and improve survival in stage III resected melanoma patients.[4] Both IFNa and ipilimumab are associated with numerous serious and life-threatening adverse effects, which are experienced to some degree by the majority of patients.[5,6] As a result, risk-benefit ratio of IFNa and ipilimumab therapies in patients with early stage melanoma is exceedingly high and the use of these agents in patients with stage I and II melanoma cannot be recommended. Interferon is not currently approved for use in the majority of Stage IIB patients of which approximately one-third will recur. Even for Stage IIC patients in whom Interferon can be given, the toxicity profile is often such that most investigators will not use it. Therefore, there is an unmet need for adjuvant therapy in patients with high-risk Stage IIB and IIC melanoma.

Given the efficacy and toxicity profile of anti-PD1 antibodies such as nivolumab and pembrolizumab in the metastatic setting, adjuvant trials involving PD-1 blockade are ongoing for high-risk (predominately Stage III) melanoma patients (Table 1). As approximately 70% of patients with stage I and stage II melanoma are cured with surgery alone, none of these trials testing anti-PD1 based regimens include this patient subset.

Table 1. Phase III Ongoing and Pending Adjuvant Trials

Trial	Stages	Outcome	Therapy	Status
E1609	IIIB-IV	OS	High dose or low dose Ipilimumab vs IFN-α	Active, not recruiting
KEYNOTE-054	III	RFS	Pembrolizumab vs Placebo	Active, not recruiting
CheckMate 238	IIIB-IV	RFS	Nivolumab vs Ipilimumab	Active, not recruiting
SWOG1404	III-IV	OS & RFS	High-dose IFN or Ipilimumab vs Pembrolizumab	Recruiting
EORTC18081	IIA-IIC	RFS	PEG-IFN-α2b vs observation	Active, not recruiting
EORTC18991	III	DMFS	PEG-IFN-α2b vs observation	Completed
***BRAF* mutated**				
BRIM8	III	DFS	Vemurafenib vs placebo	Active, not recruiting
COMBI-AD	III	RFS	Dabrafenib + Trametinib vs placebo	Active, not recruiting

1.2.3. Adjuvant anti-PD1 therapy is a promising treatment strategy for patients with early stage melanoma

Newer immunotherapeutic agents such as nivolumab, though not without side effects, possess a better safety profile than ipilimumab and high dose IFNa, with greater efficacy in the metastatic setting.[7,8] Importantly, immune checkpoint inhibitors function by modifying the immune response to cancer rather than acting on tumor cells directly. This mechanism is particularly important in the adjuvant setting, when tumor burden is at a microscopic level where immunotherapy may provide

the greatest opportunity for cure.

We propose a phase II single arm, multicenter clinical trial of adjuvant nivolumab for patients with stage IIB and stage IIC cutaneous melanoma. Given emerging data regarding alternative dosing schedules of nivolumab and given the logistical challenges faced by patients with every two week treatments, patients will receive nivolumab 480 mg as a flat dose IV over at least 30 minutes every 4 weeks for 48 weeks[9].

1.3. Correlative Studies

In this study, we will collect both tumor tissue and peripheral blood samples for correlative studies.

Because even thin early stage melanomas may have metastatic potential, accurate assessment of relapse risk is critical because it may accurately identify those who may benefit from early intervention. To identify this high-risk population, numerous prognostic markers within early stages of melanoma have been evaluated, including the characteristics of the primary tumor, such as thickness, mitotic rate, ulceration, and presence of an immune infiltrate. However, these criteria are inadequate to reliably differentiate those who ultimately develop metastases.[10] The prognostic utility of the sentinel lymph node biopsy (SLNB) for intermediate thickness (1-4mm) melanoma is also limited, as the procedure is unable to predict the occurrence of two out of three metastatic events.[11,12]

The emergence of novel and potentially more accurate prognostication tools combined with the availability of newer effective therapeutic agents with less toxicity than with previously available agents provides us a tremendous opportunity to identify those patients with early stage melanoma who, despite histologic characteristics, have a high risk of relapse, and to offer them a systemic therapeutic option. Large-scale genomic profiling in melanoma may enable staging of the disease on a molecular basis, with several assays available commercially and in development which may be more accurate for prognostication than more commonly used histologic criteria.[10]

Although such comprehensive molecular profiling may permit us to more accurately assess risk of recurrence in patients with early stage melanoma, significant challenges exist in what assays can be performed on the limited amount of tumor material available from thin and intermediate depth primary melanoma specimens. More limited testing using platforms such as NanoString has been feasible in primary melanoma samples.[13] Our group is currently working to evaluate the feasibility of quantitative proteomics on such limited material.

1.3.1 Tissue Based Studies

We will prospectively collect baseline archived tumor specimens (tumor block preferred; 10-20 unstained slides also acceptable) for use in prognostic biomarker development that may include, but is not limited to, routine histological and immunohistological markers, gene expression assays, and proteomic signatures. We will assess additional established and promising predictive and prognostic melanoma biomarkers.[13-15] All primary melanomas will be evaluated for presence of PDL-1 expression and evaluation of lymphocytic infiltrate, both which will be correlated with clinical outcomes. Such testing may be conducted by investigators at any of the participating centers or elsewhere upon agreement of the study leadership team. Additionally, if a patient develops a recurrence and undergoes biopsy and has agreed to have a tissue sample collected, we will make attempts to obtain a sample at the time of biopsy to assess PDL-1 expression to determine whether this expression changes after adjuvant anti-PD-1 treatment.

1.3.2 Blood Based Studies

For subjects who agree, we will collect blood samples for research studies at baseline, every 3 months

during the course of active treatment, and every 6 months subsequently through Month 24 of follow up. In adjuvant trials, standard evaluation of immune activity in cancer is not possible due to absence of measurable disease. Thus, response to therapy should be measured by using surrogate markers, such as the enzyme-linked immunosorbent spot (ELISPOT), intracellular cytokine staining (ICS) and human leukocyte antigen (HLA)-peptide multimer staining assays in patients with HLA2 phenotype (about 25% of all patients).

We will analyze both cellular and soluble biomarkers in multiplex assays as exploratory studies. Using the strategies outlined in detail below, which will be conducted in the laboratory of Dr. Geskin, we will characterize the effects of immunotherapy on building tumor-specific responses. Using our approach, we are likely to discover important highly relevant markers for disease activity such as Th1/Th2/Tr bias pre- and post-immunization changes within the CD4+ T cell compartment using broader screening methods.

Multicolor Flow Cytometry: PBMCs will be isolated to evaluate and compare pre and post treatment absolute lymphocyte counts and numbers and activation state of circulating T-cells (IFNγ+CD4+ and IFNγ+CD8+), NK cells (CD3, CD56, CD16, CD69, NKG2D); circulating T-regulatory cells (T-reg, CD4+CD25highFoxP3+) and myeloid derived suppressor cells (MDSCs (CD14-/CD33+/CD11b).

Serum profiling: We will perform exploratory Luminex 30-plex testing of sera from treated patients to explore the systemic effects of immunotherapy. We will perform broad screening for a previously identified pro-inflammatory cytokines and other immune mediators for correlation with clinical and immune outcomes. Selected serum biomarkers will be tested using a multiplex Luminex 100 (Bio-Rad Bio-Plex System) and will include the Human 16-Plex Custom Kit (IL-1α, IL-1β, IL-2, IL-2R, IL-6, IL-8, IL-10, IL-17, TNF-α, IFN-α, MIP-1α, MIP-1β, IP-10,VEGF).

We will also assess circulating tumor cells (CTC), circulating tumor DNA (ctDNA), and exosomes as part of this trial. Dr. Mahesh Mansukani, Director of the Division of Personalized Genomic Medicine in the Department of Pathology and Cell Biology at Columbia University Medical Center, will lead the ctDNA efforts. Dr. Alex Rai, Director of the Special Chemistry Laboratory in the Department of Pathology and Cell Biology at Columbia University Medical Center, will lead the exosome effort.

2. STUDY OBJECTIVES

2.1. Primary Objective

To assess the efficacy nivolumab administered in the adjuvant setting in patients with resected stage IIB or stage IIC cutaneous melanoma.

2.2. Primary Endpoint

- The primary end point is recurrence-free survival at 24 months. Recurrence-free survival time is defined as the number of days from study registration until documented progression or death without documentation of disease progression.

2.3. Secondary Objectives /Endpoints

- To evaluate and estimate the median duration of overall survival (OS) in Stage IIB-IIC melanoma patients.
- To evaluate and estimate the median duration of distant metastases-free survival (DMFS) in Stage IIB-IIC melanoma patients.
- To assess safety and toxicity using CTCAE V5.0

- To assess quality of life using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) quality of life instrument

2.4. Exploratory Objectives

- To assess and compare clinical, histological, immunological and molecular panels as prognostic and predictive biomarkers.

3. STUDY DESIGN

3.1. Characteristics

We will conduct a phase II single arm, multicenter clinical trial of adjuvant nivolumab in patients with resected American Joint Committee on Cancer stage IIB or IIC cutaneous melanoma (AJCC 8th edition).

Patients with new diagnosis of melanoma will be diagnosed and staged (including a negative sentinel lymph node biopsy or failed sentinel lymph node mapping) as per standard of care. Demonstration of lack of metastatic disease will be required prior to initiation protocol therapy. This can be via PET/CT or CT Scan of the Chest, Abdomen, and Pelvis. Patients with stage IIB and IIC melanoma will be identified and screened for eligibility within 6 months of the diagnosis. We will ask that patients consent to provide archived tumor material from the primary melanoma for the conduct of correlative studies.

3.2. Study Population

Subjects with resected American Joint Committee on Cancer stage IIB or IIC cutaneous melanoma, 18 years of age or older, will be eligible for this study within 6 months of diagnosis and within 120 days of sentinel lymph node biopsy (or failed sentinel lymph node mapping). See Section 4 for the key inclusion and exclusion criteria.

3.3. Number of Participants

We will require enrollment of 63 evaluable patients. To account for potential loss to follow up of 15%, our target number of enrolled subjects is 73. (See section 9.3. Sample Size Considerations below.) Enrollment will be competitive across all sites.

3.4. Dose and Duration of Therapy

Patients will receive nivolumab 480 mg as a flat dose IV over at least 30 minutes every 4 weeks for a total of 12 doses over the course of 48 weeks.

3.5. Duration of Follow Up

The duration of the follow up period will be 48 months.

3.6. Study Timeline

3.6.1. Primary Completion

We anticipate an accrual rate of 3 to 4 patients per month once all participating center are activated and will require 24 months for accrual with up to another 24 months of follow-up, for a total of 4 years required for primary completion.

3.6.2. Study Completion

We anticipate initiation of correlative studies between months 12 and 24, with completion of all correlative studies by 4 years.

4. STUDY ENROLLEMET AND WITHDRAWAL

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

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

1. Patients must have completely resected (as per standard of care) melanoma of cutaneous origin in order to be eligible for this study. Patients must be classified as Stage IIB or IIC cutaneous melanoma using the American Joint Committee on Cancer eighth edition. Patients with melanoma of mucosal or other non-cutaneous origin are not eligible. Patients with melanoma of ocular origin are not eligible.
2. Patients must have a negative sentinel lymph node biopsy or undergo a failed attempt at sentinel lymph node biopsy including lymphoscintigraphy which fails to show a sentinel lymph node from the melanoma primary site .
3. Patients must have systemic cross-sectional imaging (PET/CT or CT of chest, abdomen, and pelvis) which shows no evidence of metastatic disease.
4. Patient must be able to comprehend and sign a written informed consent and be willing to comply with all study procedures.
5. Men and women ≥18 years of age will be eligible.
6. Patients must have an ECOG performance status of 0 or 1.
7. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500 microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 10 g/dL.
8. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and SGOT (AST) and SGPT (ALT) and alkaline phosphatase ≤ 2 x IULN.
9. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 x ULN OR measured or calculated creatinine clearance ≥ 60 mL/min.
10. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts (≥ 350 mm3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off anti-viral therapy so long as they meet the CD4 count criteria.
11. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method for the course of the study through 120 days after the last dose of study medication. If a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she must inform her treating physician immediately. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures. Patients must not be pregnant or nursing due to unknown teratogenic side effects
12. Therapy must be initiated within 120 days of surgical resection of the sentinel lymph nodes

and within 6 months of initial diagnosis.

13. Patients must be willing to have archived tumor specimens utilized for correlative studies if available.

4.1.2. Exclusion Criteria

1. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, lobular carcinoma of the breast in situ, atypical melanocytic hyperplasia or melanoma in situ, adequately treated Stage I or II cancer (including multiple primary melanomas) from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years
2. Current immunosuppressive therapy including >10mg/day of prednisone within 14 days of enrollment is not permitted. Inhaled or topical steroids, and adrenal replacement steroid doses ≤10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
3. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.
4. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
5. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
6. Patients must not have received live vaccines within 42 days prior to registration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
7. Patients must not have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the trial results, interfere with the patient's participation for the full duration of the trial, or indicate that participation in the trial is not in the patient's best interests, in the opinion of the treating investigator.
8. Patients must not be pregnant or lactating.
9. Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) is not permitted.
10. Treatment with any investigational agent within 14 days of first administration of study treatment is not permitted.

4.2. Sub-site Enrollment Procedures

When a potential patient is identified at the sub-site, the Thomas Jefferson University (TJU) Study Site Contact must be contacted within 1 business day via email or phone. Please see the Site Contact List for email and phone number for the TJU Study Site Contact.

1. Notify them of the pending patient registration
2. Email registration documents to TJU Study Site Contact
3. Communicate the desired timeline of the registration.

The sub-site must include the eligibility checklist, signed informed consent, and any applicable documentation supporting eligibility.
Once eligibility has been confirmed locally, TJU will email the Research Coordinator at the sub-site site to confirm patient is eligible and can be enrolled onto the study. The participant will then be assigned a registration number. This number is unique to the participant on this trial and must be used moving forward.

A master study enrollment log will be maintained by the study team at Thomas Jefferson University. The sub-site site will also be asked to maintain an enrollment/screening log on-site, and email this information to the TJU Study Site Contact at least once a month. Patients cannot be registered to this study on the weekends. If a patient is to be registered on a Friday, the sub-site will need to contact the TJU Study Site Contact by Friday at noon at the latest.

If a patient is enrolled at the sub-site without approval from the lead site, TJU will:

1) Temporarily suspend the sub-site
2) Complete mandatory re-training of staff at the sub-site on the enrollment process. This training will be fully documented.

If enrollment without approval occurs a second time, the sub- site will not be able to continue to participate in this study.

4.3 Strategies for Recruitment and Retention

Potential subjects with Stage IIB and IIC melanoma will be identified by the examining physician at all sites and referred for evaluation by the principal investigator or one of the co- investigators.

The majority of completed and ongoing melanoma adjuvant clinical trials in the US have involved patients with higher risk stage III disease who are co-managed by medical oncologists, surgical oncologists and dermatology. The enrollment and accrual for these trials were typically driven by medical oncologists with longstanding referral patterns, well-established collaborative groups, and occurred at highly developed Centers of Excellence for melanoma care.

The trial we are proposing is distinct from other adjuvant melanoma trials in that the patients we will enroll are commonly managed primarily by dermatologists and/or surgical oncologists, with less common involvement of medical oncology. Many of these patients never see a medical oncologist unless they develop metastatic disease. Thus, the established mechanisms for the conduct of adjuvant clinical trials in melanoma are not sufficient for this study, and new mechanisms must be put in place to ensure successful accrual. The centers selected for participation in this trial have established melanoma disease management teams that will allow prospective identification of potential candidates by dermatology or surgical oncology, with referral to medical oncology when appropriate. Surgical oncology champions have been identified at each institution to assist with patient recruitment and enrollment.

4.4. Participant Withdrawal

4.4.1. Reasons for withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.5. Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, the Investigational New Drug (IND) sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5. STUDY INTERVENTION

5.1. Study Product

The study product is nivolumab.

5.2. Study Product Description

Nivolumab is a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. The PD-1 receptor is a key regulator of T-cell activity that has been shown to control tumor-specific inhibition of T-cell responses to tumors. Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that potentiates in vitro T-cell responses through dual ligand blockade of PD-L1 and PD-L2, and does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC). Expression of PD-L1 and PD-L2 by malignant cells or other cells, including immune cells, allows multiple tumor types to evade immune-mediated destruction. Nivolumab restores T-cell activity either by preventing inactivation or by reactivating T cells to mount a direct T-cell immune attack against tumor cells, including an increase in cytotoxic CD8 T cells in the tumor, without any measurable increase in activated circulating T cells peripheral to the tumor.

5.2.1. Acquisition

Bristol-Myers Squibb (BMS) will provide nivolumab directly to each site.

5.2.2. Formulation, Packaging, and Labeling

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (TweenTM 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

5.2.3. Product Storage and Stability

Unopened Vial

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. Do not use nivolumab after the expiry date, which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 8 hour period under room temperature and room light conditions includes the product administration period.

5.3. Dosage, Preparation, and Administration

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol- specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

In addition, nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk.

5.4. Study Product Accountability

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

1. Amount received and placed in storage area.
2. Amount currently in storage area.
3. Label ID number or batch number and use date or expiry date.
4. Dates and initials of person responsible for each nivolumab inventory entry/movement.
5. Amount dispensed to and returned by each subject, including unique subject identifiers.
6. Amount transferred to another area/site for dispensing or storage.
7. Non-study disposition (e.g., lost, wasted, broken).
8. Amount destroyed at study site.

5.5 Dose Modification and Dosing Delays

Dose modification of nivolumab is not permitted in this study. In some circumstances, it may be

necessary to temporarily interrupt study treatments as a result of AEs that may have an unclear relationship to the study drug.

Treatment must be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities) or selected ≥ grade 2 immune-related toxicities, and severe or life-threatening AEs. Treatment can be held for up to 8 weeks from date of last treatment. If steroids are needed, participant should be treated but if treatment must be withheld for greater than 8 weeks, participant must be permanently discontinued from study treatment.

Table 2 summarizes the dose administration guidance for nivolumab that must be implemented with the indicated related AEs. Additional information related to dose changes for nivolumab for specific AEs can be found subsequently.

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT OR total bilirubin values meeting discontinuation parameters must have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Lead Study PI.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Lead Study PI. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Table 2: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing of Treatment Restart	Nivolumab	Discontinue Subject
Hematologic Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose for the following events: Grade 4 neutropenia lasting ≤ 7 days, Grade 4 lymphopenia or leukopenia.	Toxicity dose not resolve within 6 weeks of last infusion. Permanent discontinuation must be considered for any severe or life-threatening event.

				For all other Grade 4 Hematologic toxicities treatment with nivolumab may not be restarted.	
Non-Hematologic Toxicity **Note: Exception to be treated similar to Grade 1 toxicity: - Grade 2 alopecia - Grade 2 fatigue - Grade 3 rash in the absence of desquamation, without mucosal involvement, not requiring systemic steroids, and that resolves to Grade 1 within 14 days** ** See section 5.5. for immune-related AE's*	1	No	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation must be considered for any severe or life-threatening event.
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation must be considered for any severe of life-threatening event.
	4	Yes	Discontinue treatment	Treatment with nivolumab may not be restarted	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation must be considered for any severe of life-threatening event.

Note: Subjects who experience a recurrence of the same severe or life-threatening AE at the same grade or greater treatment must be discontinued from study treatment.

If treatment for a participant needs to be held in a situation that is not the result of toxicity (non-toxicity scenario), treatment can be held for up to 8 weeks. If treatment needs to be held for a period greater than 8 weeks, the participant should be permanently discontinued from study treatment.

If treatment is held, regardless if for toxicity or non-toxicity, the missed dose is considered skipped and will not be made up.

5.5.1 **Study Drug Discontinuation**

Treatment with Nivolumab will be discontinued if treatment cannot be tolerated (toxicity), due to disease progression, or for whom treatment could not be resumed after non-toxicity related hold (see Section 5.5).

Those subjects who discontinue from treatment regardless of reason will be followed as described in section 6.1. Time and Events Schedule.

See Section 7.2 for handling of participants who withdraw from the study.

5.6 Expected Toxicities for Nivolumab

Expected toxicities for monotherapy Nivolumab are listed below.

Common side effects of nivolumab are: (≥ 10%)

- Fatigue
- Rash
- Diarrhea

- Nausea
- Itching, burning, numbness or weakness, possibly in arms, legs, hands, and feet
- Thyroid gland function change
- Joint pain or stiffness

Side effects of Nivolumab are: (≥ 1%)

- Increased Alkaline phosphate, ALT (alanine aminotransferase) an/or AST (aspartate aminotransferase)
- Amylase increased
- Creatinine increased
- Decreased appetite
- Dry Mouth
- Inflammation of the colon and mouth
- Dry skin
- Loss of color (pigment) from areas of skin
- Swelling, including face, arms, and legs
- Fever
- Headache
- Infusion related reaction
- Lung inflammation (pneumonitis – see additional information below)

Uncommon side effects of Nivolumab are: (≥ 0.1%)

- Change in hormones
- Allergic reaction
- Bronchitis
- Respiratory failure
- Disturbance of nerves
- Vertigo (a sensation of feeling off balance; dizziness)
- Heart rate increased
- Hypertension (increased blood pressure)
- Hives
- Dry eye
- Hair loss
- Inflammation of the eye, heart, kidney, pancreas, pituitary gland, stomach, thyroid gland, liver
- Renal failure
- Blurred vision
- Hepatitis
- Inflammation of the heart

Rare side effects of Nivolumab are: (≥ 0.01%)

- Lipase increased (lab test result associated with pancreas inflammation)
- Abdominal pain
- Increased liver function test

- Decreased appetite
- Encephalitis
- Pericardial effusion
- Pericarditis
- Enteritis
- Constipation
- Asthenia
- Immune-mediated hepatitis
- hypertransaminasaemia
- Anaphylactic reaction (severe allergic reaction)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids
- Skin inflammatory reaction, including serve reaction
- Guillian-Barre syndrome – an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels, brain, potentially life-threatening
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles
- Polymyalgia rheumatic
- Rhabdomyolysis – muscle fiber released into the blood stream
- Rosacea
- Sarcoidosis – a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis – disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.

Lung Inflammation (Pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with X-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increase rate of breathing, fever, low blood oxygen levels, or fatigue.

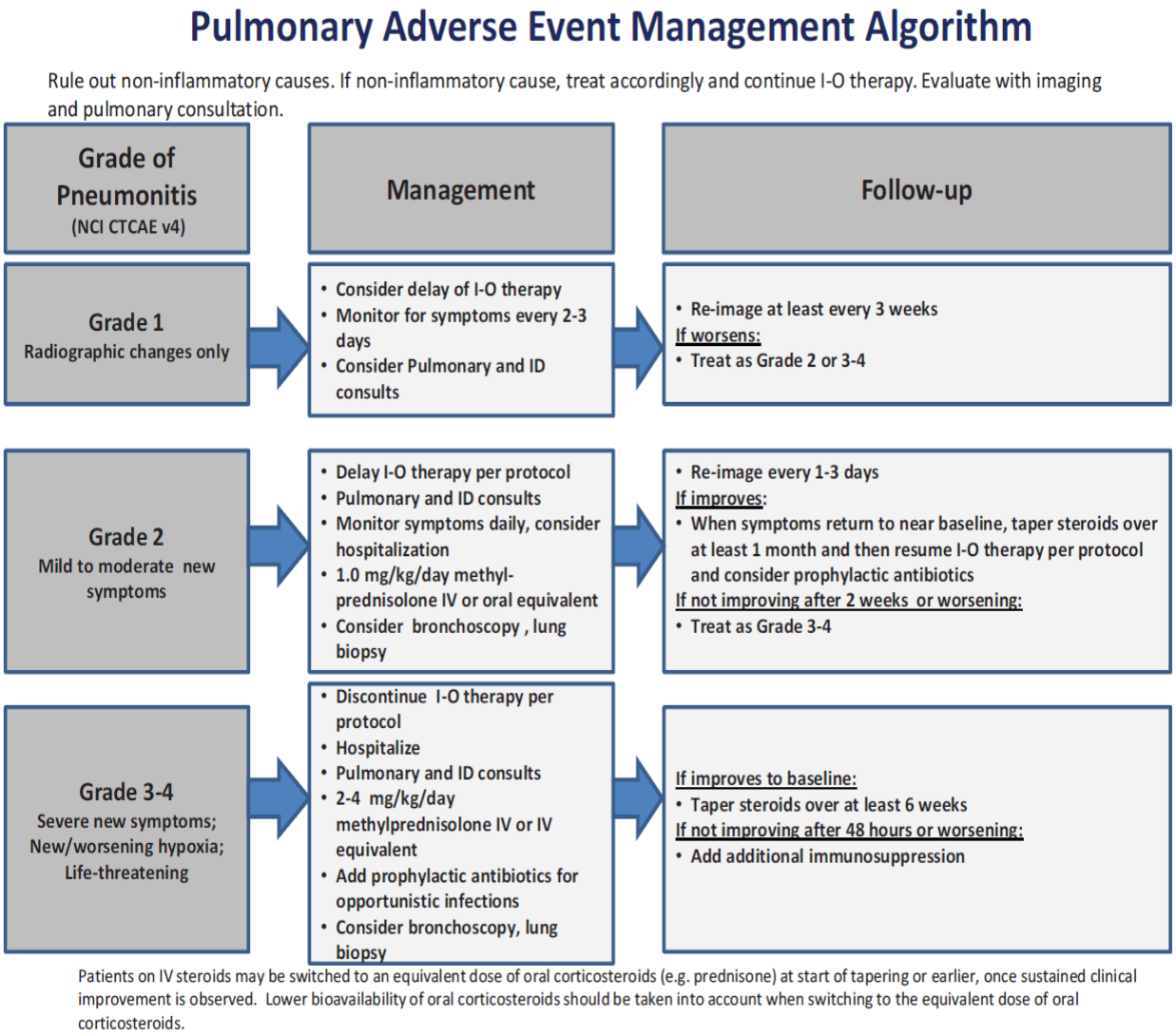
5.7. Procedures for Subjects Exhibiting Immune-Related Adverse Events

Immune-related AEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the nivolumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention must be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

Recommendations for management of specific immune-mediated AEs such as pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and other immune-mediated AEs are detailed in the sections below.

5.7.1. Procedures and Guidelines for Pneumonitis

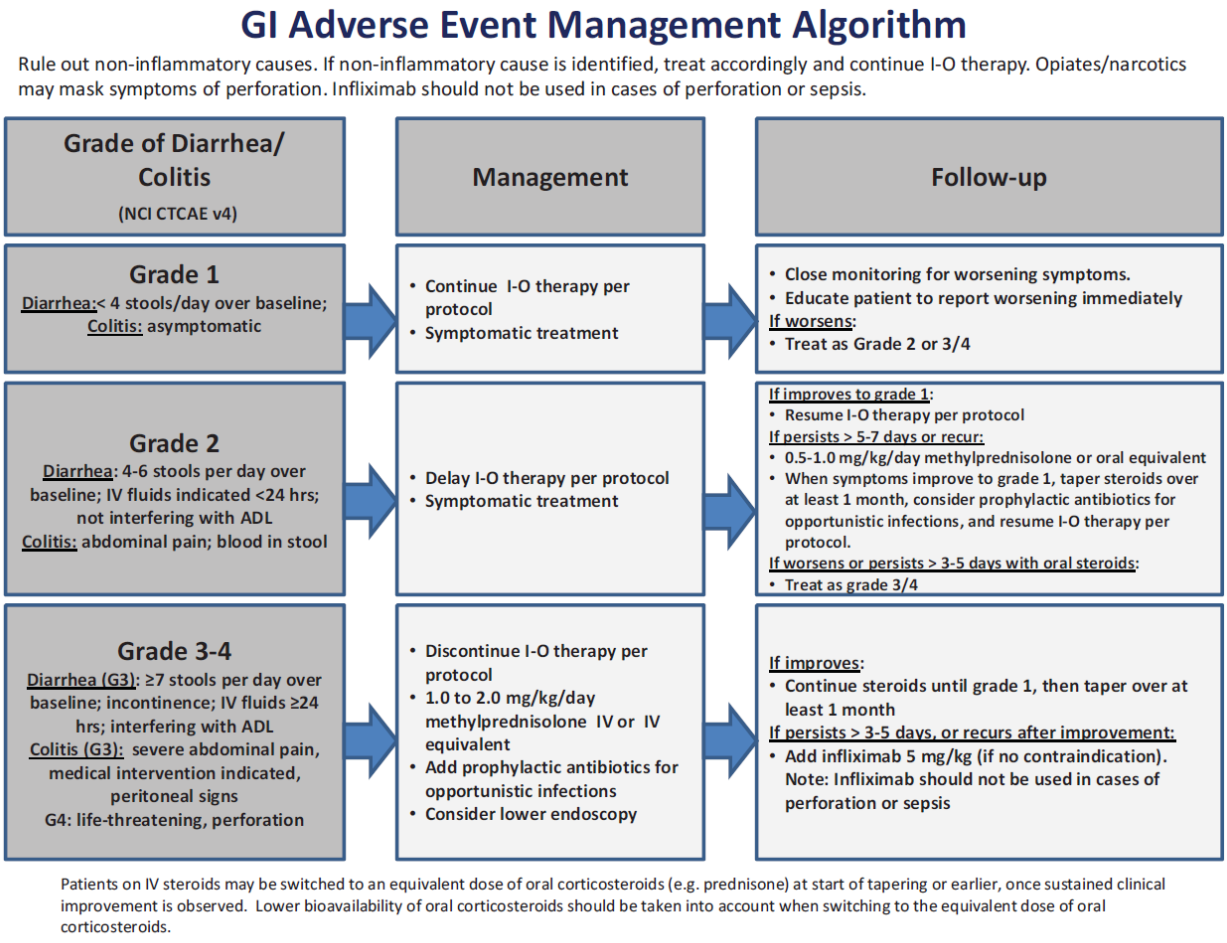
Subjects with symptomatic pneumonitis must immediately stop receiving nivolumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug–associated pneumonitis, the suggested treatment plan is below.



5.7.2. Procedures and Guidelines for Enterocolitis

Subjects must be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out and endoscopic evaluation must be considered for persistent or severe symptoms. Recommendations for

management of enterocolitis are shown below.

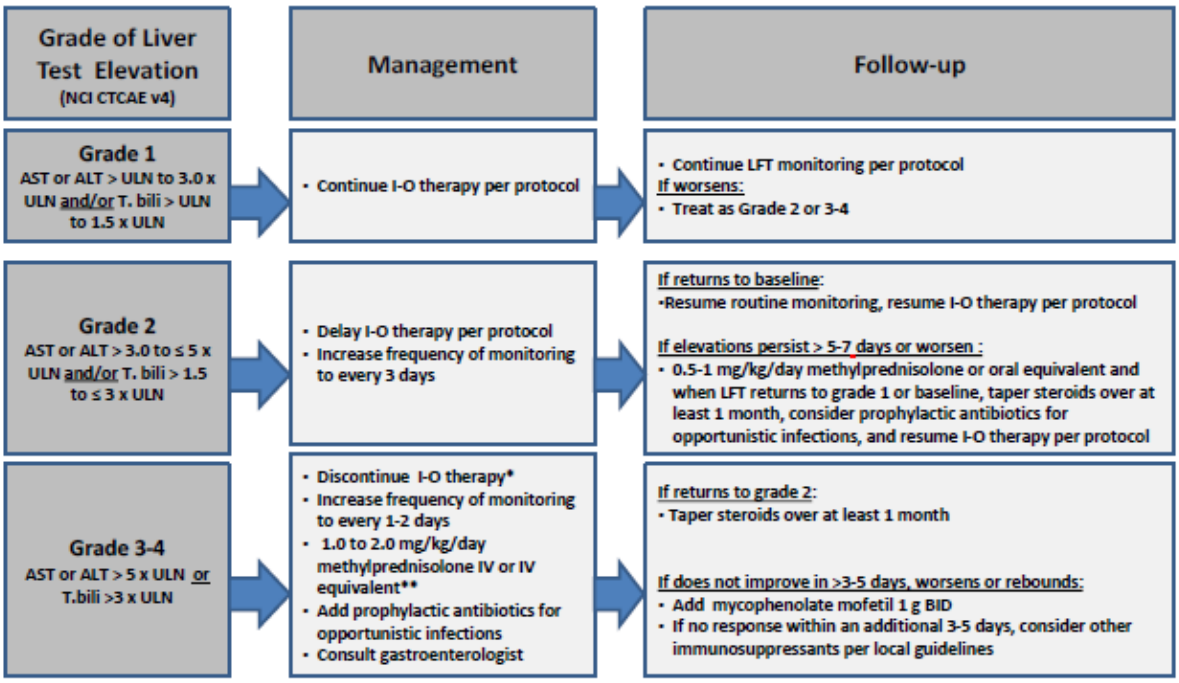


5.7.3. Procedures and Guidelines for Hepatitis

Liver function tests (hepatic transaminase and bilirubin levels) must be monitored and signs and symptoms of hepatotoxicity must be assessed before each dose of nivolumab. In subjects with hepatotoxicity, infectious or malignant causes must be ruled out and frequency of LFT monitoring increased until resolution. Recommendations for management of hepatitis are shown below.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



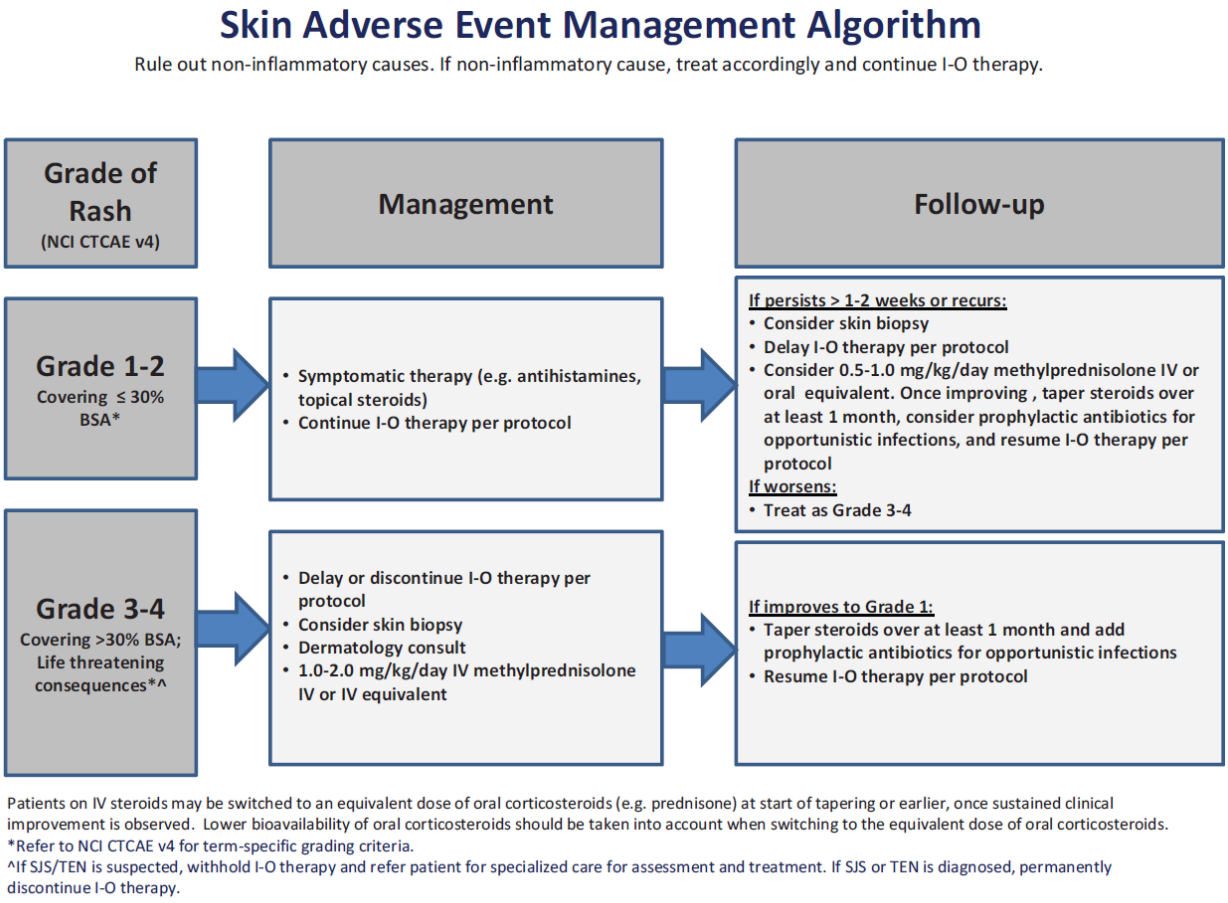
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

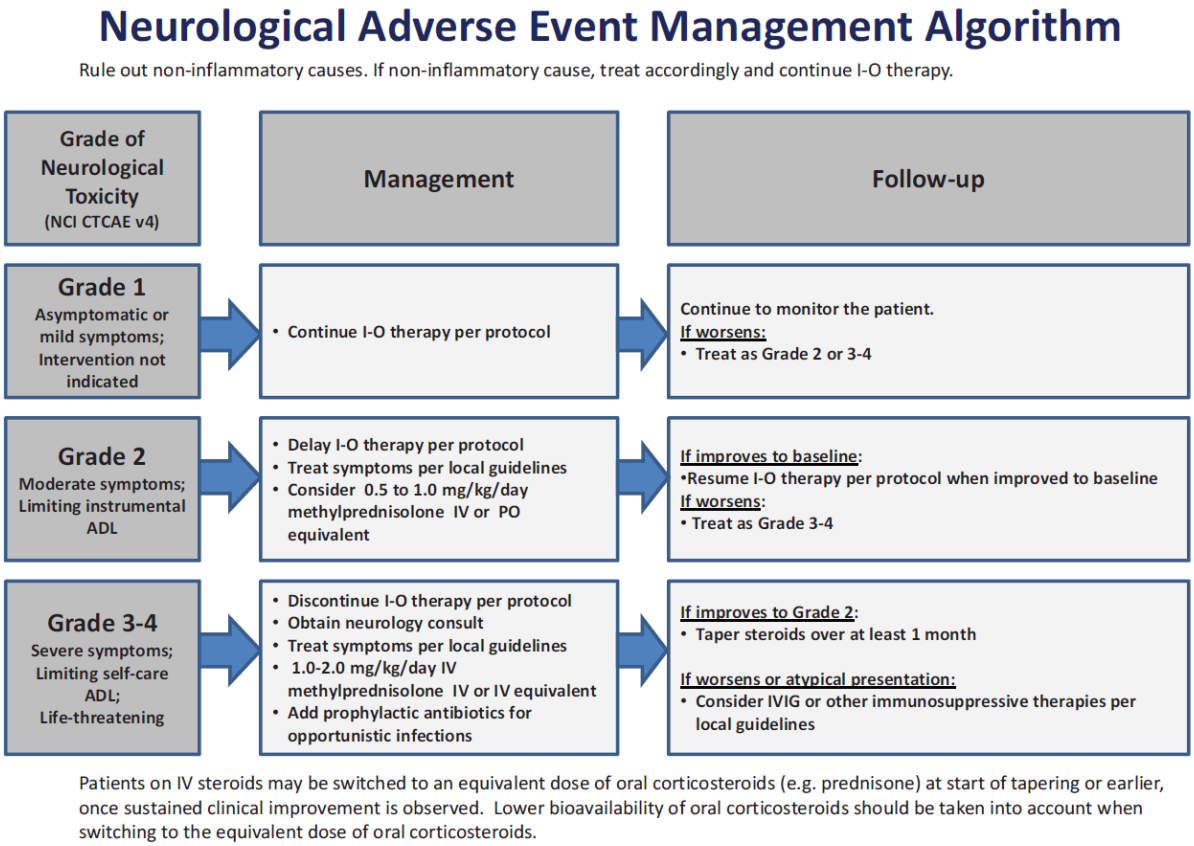
5.7.4. Procedures for Immune-Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis must be considered immune mediated. Recommendations for management of dermatitis are shown below.



5.7.5. Procedures for Immune-Mediated Neuropathies

Subjects must be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or parenthesis. Recommendations for management of neuropathies are shown in table below.



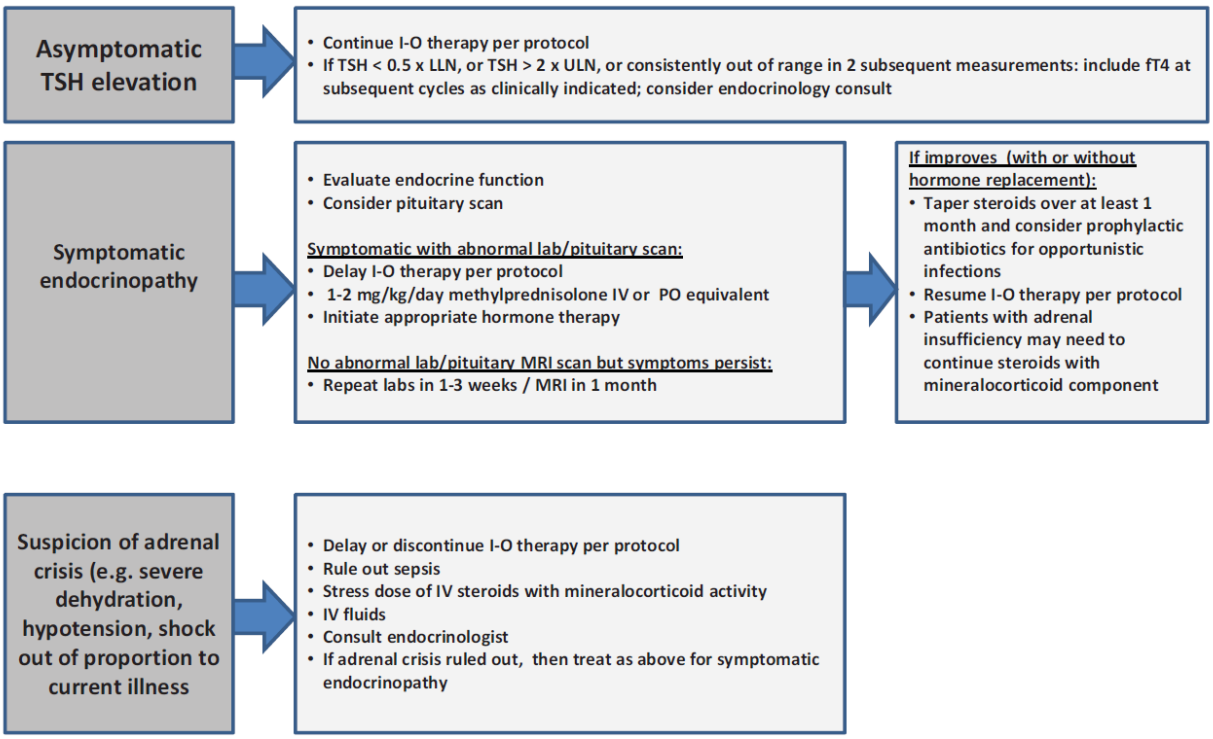
5.7.6. Procedures for Immune-Mediated Endocrinopathies

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

Thyroid function tests and clinical chemistries must be monitored at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Recommendations for management of endocrinopathies are shown below.

Endocrinopathy Management Algorithm

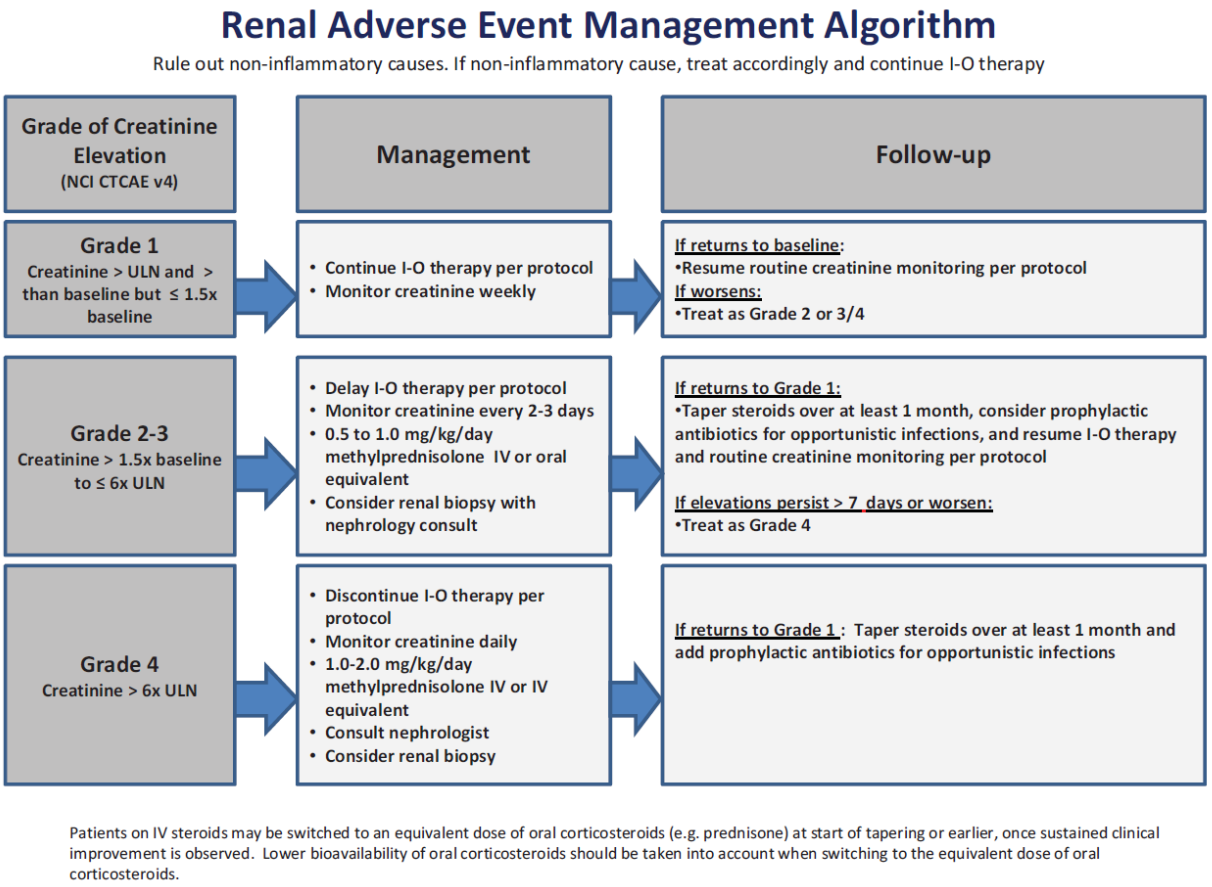
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

5.7.7. Procedures for Immune-Mediated Nephritis

Renal function tests (creatinine) must be monitored and signs and symptoms of nephrotoxicity must be assessed before each dose of nivolumab. In subjects with nephrotoxicy, infectious or malignant causes must be ruled out and frequency of Creatinine monitoring increased until resolution. Recommendations for management of nephritis are shown below.



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

5.7.8. Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

Nivolumab must be permanently discontinued for severe immune-mediated adverse reactions. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse reactions.

Corticosteroid eye drops must be administered to subjects who develop uveitis, iritis, or episcleritis. Nivolumab must be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.8. Dietary Restrictions

Patients on a controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

6. STUDY SCHEDULE

6.1. Time and Events Schedule

Table 3. Time and Events Schedule is on the following page.

	Screening	Treatment Cycle (4 Week Cycle) [a]												Follow up (months) [k]									End of Treatment (EOT)/ Withdrawal[m]
														M1 Post-Scans	Every 3 months from last Infusion x 1 year				Every 6 months subsequently x2 years			Final Year	
	28 Days*	1	2	3	4	5	6	7	8	9	10	11	12		M3	M6	M9	M12	M18	M24	M30	M36	M42 and M48	
Informed Consent	X																						
History and Physical Exam[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	x	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Beta HCG Pregnancy Test[c]	X	X	X	X	X	X	X	X	X	X	X	X	X											
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cross-sectional imaging, including at minimum chest, abdomen and pelvis[e]	X							X						X		X		X	X	X	X	X	X	X[l]
AE Assessment		Assessed at every visit																						
Research blood sample collection[f]	X[j]	X[j]			X			X			X			X		X		X	X	X				X
CTC Analysis[g]	X[j]	X[j]			X									X										
Quality of Life Assessment (Appendix #1)		X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X	X
Nivolumab Therapy		X	X	X	X	X	X	X	X	X	X	X	X											
Archived tissue request	X																							

*Screening period is a total of 28 days; Screening labs that are performed within 7 days prior to C1D1 do not need to be repeated

a. Treatment may be administered with a window of ± 7 days.

b. Visits may be performed with a window of ± 14 days. Long-term follow up may be discontinued once the primary end point is assessed and met.

c. If female of childbearing potential, a pregnancy test will be required at screening visit and prior to the start of each cycle of study drug.

d. Laboratory Assessments:

- Hematology labs to include hemoglobin, hematocrit, red blood cell count, white blood cell count, platelets (direct platelet count), as well as total and differential CBC counts. The CBC differential includes enumeration of neutrophils, lymphocytes, eosinophils, monocytes, basophils and any abnormal blood cells noted in the differential.
- Chemistry laboratory analysis includes albumin, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, total bilirubin, TSH, glucose, total protein, sodium, potassium, chloride, and CO2.
- Hematology, chemistry and endocrine laboratory analysis to be performed within 7 days prior to each Nivolumab treatment

e. CT or PET/CT imaging will be performed after the 6th infusion (prior to treatment cycle 7) and after the 12th infusion (prior to month 1 Follow-up). All scans during the 24 month follow-up period should be performed 6 months after last previous scan and at the discretion of the treating physician. After 24 months of follow-up, scans will be performed per standard of care or the discretion of the treating physician. If a participant discontinues treatment for any reason, including disease progression, scans and visits will resume at the next scheduled timepoint as indicated in the table.

f. Research blood samples are optional for subjects. Samples will be drawn any time within the 28 day screening period up until pre-dose C1D1, every 3 months during nivolumab therapy, and then every 6 months thereafter through Month 24 of follow up.

g. CTC analysis samples are optional for subjects. Samples will be drawn any time within the 28 day screening period up until pre-dose C1D1, at 3 months, and 12 months.

h. Patients will be monitored for local or regional recurrence based on physical examination at their treatment visits and cross-sectional imaging.

i. Screening labs and physical performed as part of screening can be used to satisfy Cycle 1 Day 1 requirements if completed within 7 days of first treatment

j. Research Study samplesand CTC Analysis can be collected any time during the screening period up until pre-dose Treatment Cycle 1.

k. For the follow up visits occurring after the M1 visit can occur ±6 weeks

l. Per standard of care, performed if clinically indicated. Or if scans were done within 8 weeks, reports and images will be obtained.

m. For patients who discontinue treatment due to disease progression, they will be followed only for survival every 3 months starting from the EOT visit. If information is available on subsequent treatments, this will be collected.

7. STUDY PROCEDURES AND EVALUATIONS

7.1. Procedures by Visit

The Time and Events Schedule (Table 3) summarizes the frequency and timing of various measurements.

Eligible patients will be consented, enrolled and treated on study. Patients will receive nivolumab 480 mg as a flat dose IV over at least 30 minutes every 4 weeks for a total of 12 doses over the course of 48 weeks. During these 48 weeks, patients will be seen in clinic monthly prior to each infusion for interval history and physical examination, with routine bloodwork obtained including a CBC, comprehensive metabolic panel, TSH and LDH. Subsequently, patients will be seen on an every 3 month basis through month 24 of the study, and every 6 months though month 60 of the study. Cross-sectional imaging including a chest, abdominal and pelvic CT imaging (or PET/CT imaging) will be performed after the 6th infusion (prior to the start of Cycle 7) and after the 12th infusion (prior to month 1 Follow-Up). All scans during the 24 month follow-up period should be performed every 6 months after the last previous scan and at the discretion of the treating physician. After 24 months of follow-up, scans will be performed per standard of care or the discretion of the treating physician. If a participant discontinues treatment for any reason, including disease progression, scans and visits will resume at the next scheduled timepoint as indicated in in Section 6.1. Participants who discontinue treatment due to disease progression will have an End of Treatment (EOT) visit and will be followed for only survival every 3 months from that visit (see Section 6.1). An optional tissue sample may be collected at the time the time of recurrence, if patients have agreed and a biopsy is being performed.

Preserving quality of life is a critical consideration when developing therapies for conditions in which majority of the patients have favorable outcomes. This is true for patients with early stage melanoma, as nearly 70% of them are cured by surgical excision alone. During treatment, we will evaluate the quality of life prior to each treatment. During follow-up, we will evaluate quality of life every 6 months using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) quality of life instrument.

7.2 Withdrawal of Consent

Participants who request to discontinue study drug or for whom study drug must be discontinued will remain in the study and must continue to be followed for protocol-specified follow-up procedures (see Section6.1). The only exception to this is when a participant specifically withdraws consent for any further contact. Participants 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 the study drug or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that event vital status (whether the participant is alive or dead) is being measured, publically available information should be used to determine vital status only, as appropriately directed in accordance with local law.

7.3 Lost to Follow Up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. Lost to follow up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, texts, or emails as well as lack of response by the participant to 1 registered mail letter. All attempts should be documented in the participant's medical records. If it

is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.

7.4. Details of Procedures and Evaluations

7.4.1. Medical History, Physical Exam, Physical Measurements

A Medical History will be obtained at screening to ensure subject meets all inclusion and exclusion criteria. If the subject consents to be enrolled in the study, a detailed medical history will be obtained at the baseline visit. Please include in history any toxicities related to previous treatments, if applicable.

Physical examinations including weight measurement will be performed at the time points outlined in Table 3.

7.4.1.1. Vital Signs

Vital signs consist of blood pressure, heart rate, respiratory rate and temperature measurements. Vital signs will be obtained as outlined in Table 3.

7.4.1.2. Pregnancy Testing

WOCBP are required to have several pregnancy tests performed. A negative serum pregnancy test must be documented at the screening visit. Additionally WOCBP must exhibit a *negative serum or urine pregnancy test* (minimum sensitivity 25 IU/L or equivalent units of HCG) *prior to the start of each cycle of study drug.*

7.4.1.3. ECOG Status

ECOG performance status will be evaluated at the screening evaluation and at each visit.

7.3.1.4. Laboratory Test Assessments

Results of all safety laboratory collections must be obtained and reviewed in advance of study drug dosing, as applicable.

During both Treatment and Follow-up Phases, labs must be collected in the following timeframes:

- Required laboratory examinations must be collected within 7 days prior to dosing. Screening labs can be used to satisfy the C1D1 requirements if collected within 7 days of first treatment.

7.5. Research Sample Collection

For those subjects who agree to have the research samples collected, the following will be collected:

- Serum and PBMC will be collected at baseline or on C1D1 prior to treatment, every 3 months during nivolumab therapy, and then every 6 months thereafter through follow up Month 24.
- CTCs will be collected at baseline or on C1D1 prior to treatment, 3 months, and 12 months.

Additional laboratory testing thereafter will be performed at the discretion of the investigator.

At EACH time point please submit the following:

- 2 - 10 ml GREEN top tubes
- 4 - 10 ml LAVENDER top EDTA tubes
- 2 - 10 ml RED top (glass) tube

Each tube must be clearly labeled to include:

- Protocol number
- Patient sequence number
- Patient initials

- Originating institution/investigator name
- Date and time drawn
- Collection time point

See laboratory manual for additional information.

8. EVALUATION OF SAFETY

8.1. Data and Safety Monitoring Plan

A data safety monitoring plan for this study consists of monitoring the adverse events and data to evaluate the efficacy and effectiveness of the study. The SKCC DSMC will assign a medical monitor to the study who will be responsible for the day-to-day monitoring of all AEs and SAEs reported from the trial. The medical monitor will be responsible to review these at quarterly DSMC meetings and as needed. Decisions to continue or close the trial to accrual and subject recruitment, accrual and retention, and/or if the trial should continue are also discussed during these meetings. Any modifications necessary to ensure subject safety are discussed and modifica tions will be submitted to the IRB. If any literature becomes available which suggests that conducting this trial is no longer ethical, the study will be terminated and the IRB will be notified of the new findings. The IRB will be notified of any change in the risk/benefit ratio that would affect whether the study should continue. All serious adverse events will be reported to the IRB according to the established guidelines. A cumulative summary of all events occurring during this study will also be submitted to the IRB with the annual renewal report. Serious adverse events will also be reported to the sponsor and /or other regulatory agency as per their requirements.

8.2. Specification of Safety Parameters

8.2.1. Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2.2. Adverse Events

An adverse event is any untoward or unfavorable medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

8.2.3. Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it

occurred)

- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

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

- 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 (eg, 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 (eg, 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. Safety Assessment and Follow-Up

Adverse event reporting will begin after study treatment, unless AE/SAE is caused by a study specific screening procedure, and continue until30 days after the last dose of study treatment. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4. Recording Adverse Events

The following subsections detail what information must be documented for each adverse event.

8.4.1. Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)

a. The event is known to occur with the study intervention.

b. There is a temporal relationship between the intervention and event onset.

c. The event abates when the intervention is discontinued.

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset.

b. An alternate etiology has been established.

8.4.2. Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.4.3. Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
The following categories and definitions of intensity as determined by a physician must be used:

- Mild (Grade 1): Awareness of event but easily tolerated.
- Moderate (Grade 2): Discomfort enough to cause some interference with usual activity.
- Severe (Grade 3): Inability to carry out usual activity.
- Very Severe (Grade 4): Debilitating; significantly incapacitates subject despite symptomatic therapy.

8.4.4. Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4.5. Non-serious 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 [eg, IND US trial] as part of an annual reporting requirement.

Non-serious AE information must also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information must begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) must be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs must 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.

8.5. Safety Reporting

8.5.1. Reporting to the IRB

8.5.1.1. Unanticipated Problems

All incidents or events that meet criteria for unanticipated problems (UAPs) require the creation and completion of an unanticipated problem report form.

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

8.5.1.1.1

Sub-Site Unanticipated Problems Reporting

Unanticipated problems (UAPs) occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines.

UAPs occurring at the sub-site must also be reporting to Thomas Jefferson University using the Unanticipated Problems Form (see Appendix 2). The TJU Study Site Contact will submit UAPs occurring at the sub-site to the TJU IRB.

8.5.1.2. Adverse Events

Grade 1 AEs will be reported to the IRB at continuing review.
Grade 2 AEs will be reported to the IRB at the time of continuing review.

8.5.1.3. Serious Adverse Events

SAEs will be reported to the IRB.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.
All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

SAEs occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines. Section 8.5.1.4 provides information on reporting SAEs to TJU.

8.5.1.4 Sub-Site SAE Reporting

All SAEs occurring at the sub-site must be reported to the TJU Study Site Contact within 24 hours of notification. This initial notification can take place via email or phone, followed by the submission of a formal report.

SAEs must be reported to TJU using the FDA Medwatch 3500A, and must comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports must be included.

SAE Reports must be signed by the sub-site PI, and then emailed to the Thomas Jefferson University Study Site Contact within 24 hours.

The TJU coordinator will notify the TJU PI and obtain the TJU PI signature, and report these events to the TJU Medical Monitor/IRB appropriately (within 5 working days if it deems an amendment, or in a spreadsheet at the time of annual review if no amendment is necessary).

Additional follow-up SAE reports must be submitted when available.

All reportable Adverse Events (AEs) must be reported to the TJU Research Coordinator within 48 hours using the FDA MedWatch 3500 form.

A reportable AE is any adverse event NOT identified in the IB or consent form as a risk.

Any non-reportable AE must be kept by the sub-site on an ongoing tracking log to be reviewed by TJU quarterly.

Unanticipated problems (UAPs) that pose risk to subjects or others, and that are not AEs/SAEs should be reported to TJU within 5 working days using form Unanticipated Problems Form (see Appendix 2) and must be emailed to the TJU Study Site Contact within 5 business days.

8.5.2 Reporting to SKCC DSMC

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI must be reported to the DSMC.

The sub-site is required to provide copies of any Unanticipated Problems, protocol deviations, and AE logs to the TJU Study Site Contact for submission to the DSMC.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

8.5.3. SKCC Reporting SAEs to BMS

All Serious Adverse Events (SAEs) that occur following the subject's initiation of study treatment, unless AE/SAE is caused by a study specific screening procedure, through 30* days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

Following the subject's initiation of treatment, unless AE/SAE is caused by a study specific screening procedure, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator must report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

An SAE report must 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 must be specified in the narrative section of the SAE Report Form.

If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) must be used to report SAEs to BMS . The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.

- The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- The MedWatch form is available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

The sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Saftey@bms.com). Frequency of reconciliation must be every 3 months and prior to the database lock or final data summary. GMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation must 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 must be sent immediately to BMS.

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a 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 (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the 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 must also comply with the IRB/IEC procedures for reporting any other safety information.
- 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).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on either CIOMS or MedWatch form & pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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 must be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

8.5.4 SKCC Reporting to the FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.
SAEs must be reported on MedWatch Form 3500A, which can be accessed at:
http://www.accessdata.fda.gov/scripts/medwatch/.
MedWatch SAE forms must be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs must simultaneously be faxed or e-mailed to BMS at:

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

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

• For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

• 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 must be specified in the narrative section of the SAE Report Form.

• If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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 must be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization. All SAEs must be followed to resolution or stabilization.

For any fatal or life-threatening adverse event that is unexpected and assessed by the investigator as possibly related to the use of nivolumab, the sub-site must submit a completed FDA Medwatch 3500A Form and email form to the TJU study site contact for submission to the FDA and BMS. The initial communication may take place via telephone but must be followed up with the completed form within 24 hours of first learning of the event.

8.6 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

8.7 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Plan

9.1.1. Baseline Characteristics

Baseline descriptive statistics on all evaluable patients will be provided on demographic variables (age, sex, and race/ethnicity), performance status, laboratory parameters, the treatment regimens that were previously used, and disease characteristics.

9.1.2. Survival and Recurrence-free Survival

Patients' survival times will be measured from the initial date of treatment to the recorded date of death. Recurrence-free survival (RFS) will be measured from the initial date of treatment to the date of documented recurrence. Distant Metastases-free survival (DMFS) is defined as the time from definitive surgery to the date of diagnosis of metastatic disesase.

Overall survival and recurrence-free survival (RFS) will be estimated by the Kaplan-Meier method. The corresponding median survival times (with 90% confidence limits) will be determined, as will the cumulative percentage of patients remaining progression-free / alive at selected time points after initial treatment (e.g., 6, 12, and 18 months).

9.2. Interim Analyses and Stopping Rules

The Principal Investigators and coordinators will have monthly conference calls to review study data and subject safety issues. Decisions to continue or close the trial to accrual and subject recruitment, accrual and retention, and/or if the trial should continue are also discussed during these meetings. Any modifications necessary to ensure subject safety are discussed and modifications will be submitted to the IRB. If any literature becomes available which suggests that conducting this trial is no longer ethical, the study will be terminated and the IRB will be notified of the new findings. The IRB will be notified of any change in the risk/benefit ratio that would affect whether the study should continue.

9.3. Sample Size Considerations

Based upon recent retrospective analyses, the 24 month recurrence free survival rate for our patient population is 70%. To demonstrate a 50% improvement in the 24 month recurrence free survival rate (0.70 vs 0.85), with power of 0.90, alpha 0.05 using one arm non-parametric survival (one-sided) test, we will require enrollment of 63 evaluable patients. To account for potential loss to follow up of 15%, our target number of enrolled subjects is 73. We will require 24 months of follow-up for all patients for evaluation of the primary endpoint.

9.4. Accrural Estimates

With the centers selected for participation, once all sites are open for accrual, we anticipate being able to accrue 3 to 4 patients per month. We will therefore require 24 months for accrual and a total of 48 months required to evaluate the primary endpoint.

10. ETHICS/ PROTECTION OF HUMAN PARTICIPANTS

10.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

10.2. Institutional Board Review

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

10.3. Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

10.4. Exclusion of Women, Minorities, and Children (Special Populations)

Children: Because the proportional incidence of melanoma is low under 18 years of age and the fact that we do not have data to show that the experimental therapy is safe to give to children under 18 years of age, they will be excluded from this study. If new information becomes available to show the therapy has minimal risks when compared to the benefits, the protocol will be amended to include them.

Women and Pregnancy: Because the effect of the nivolumab was not studied in pregnancy the potential risks to the fetus cannot be assessed, pregnant females will not be included in the study. However, no female of childbearing potential will be excluded from the study. An effective form of contraception of the woman's choice will be required at all times during study. A pregnancy test will be performed on enrollment and monthly on an ongoing basis while the female is enrolled in the study.

Minority Enrollment: No minorities or their subpopulations will be excluded from the study. We expect the enrollment to reflect the incidence and number of minority subjects at the participating Health Systems. Every attempt will be made to encourage participation of minorities in these trials.

10.5. Participants Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

11. DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

11.1. Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

11.2. Study Records Retention

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.3. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

12. STUDY FINANCES

12.1 Funding Sources

12.2 Conflict of Interest

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

13. PUBLICATION AND DATA SHARING

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

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Appendix #1—FACT-M for quality of life assessment

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
M1	I have pain at my melanoma site or surgical site	0	1	2	3	4
M2	I have noticed new changes in my skin (lumps, bumps, color(colour))	0	1	2	3	4
M3	I worry about the appearance of surgical scars	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
ITU4	I have to limit my physical activity because of my condition	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
Hep3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
M5	I have aches and pains in my bones	0	1	2	3	4
M6	I have noticed blood in my stool	0	1	2	3	4
ITU3	I have to limit my social activity because of my condition	0	1	2	3	4
MS8	I feel overwhelmed by my condition	0	1	2	3	4
M8	I isolate myself from others because of my condition	0	1	2	3	4
M9	I have difficulty thinking clearly (remembering, concentrating)	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	At the site of my melanoma surgery:	Not at all	A little bit	Some-what	Quite a bit	Very much
M10	I have swelling at my melanoma site	0	1	2	3	4
M11	I have swelling as a result of surgery	0	1	2	3	4
M12	I am bothered by the amount of swelling	0	1	2	3	4
M13	Movement of my swollen area is painful	0	1	2	3	4
M14	Swelling keeps me from doing the things I want to do	0	1	2	3	4
M15	Swelling keeps me from wearing clothes or shoes I want to wear	0	1	2	3	4
M16	I feel numbness at my surgical site	0	1	2	3	4
M17	I have good range of movement in my arm or leg	0	1	2	3	4

Appendix #2

UNANTICIPATED PROBLEM REPORT FORM

For Sub-Site Reporting

Thomas Jefferson University Principal Investigator: _____
Sub-Site Principal Investigator: _____
TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____
_____

Subject ID: _____ Approx. Date of Problem: _____ Date Aware: ____
Description of Problem: _____
_____

Is this Unanticipated Problem a Protocol Deviation? Yes ☐ No ☐
Did the Unanticipated Problem pose risk to subjects or others? Yes ☐ No ☐
If no, have PI or Co-I sign the form. If YES, describe the risk below:

Describe the Corrective Action Plan: _____
_____
Has the problem been resolved? Yes ☐ No ☐
Does the consent or protocol require modification? Yes ☐ No ☐

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number