

**ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY**

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**PROTOCOL UPDATE TO ALLIANCE A091401**

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**RANDOMIZED PHASE II STUDY OF NIVOLUMAB WITH OR WITHOUT IPILIMUMAB IN PATIENTS WITH METASTATIC OR UNRESECTABLE SARCOMA**

*NCI-supplied agents: Nivolumab (NSC #748726, IND #126336); IND holder: CTEP  
Ipilimumab (NSC #732442, IND #126336), IND holder: CTEP*

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| <input checked="" type="checkbox"/> <b>Update:</b>                             | <input type="checkbox"/> <b>Status Change:</b>          |
| <input type="checkbox"/> Eligibility changes                                   | <input type="checkbox"/> Activation                     |
| <input type="checkbox"/> Therapy / Dose Modifications / Study Calendar changes | <input type="checkbox"/> Closure                        |
| <input type="checkbox"/> Informed Consent changes                              | <input type="checkbox"/> Suspension / temporary closure |
| <input type="checkbox"/> Scientific / Statistical Considerations changes       | <input type="checkbox"/> Reactivation                   |
| <input type="checkbox"/> Data Submission / Forms changes                       |   |
| <input checked="" type="checkbox"/> Editorial / Administrative changes         |   |
| <input checked="" type="checkbox"/> Other: Updated CAEPR for Ipilimumab        |   |

*The changes included in this update to A091401 have been made in response to the NCI Action Letters for ipilimumab from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). The Action Letter is posted on the A091401 study page on the Alliance and CTSU websites. A revised CAEPR with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.*

*Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.*

**UPDATES TO THE PROTOCOL:**

**[Section 9.4.2 \(Comprehensive Adverse Events and Potential Risks list \[CAEPR\] for Ipilimumab \[MDX-010, NSCs 732442, IND #126336\]\)](#)**

This section has an updated CAEPR for ipilimumab. Version 2.9, December 20, 2017 has been updated to Version 2.10, March 29, 2019. Changes from Version 2.9 to Version 2.10 include the following:

- Added New Risk:
  - Rare but Serious: Nervous system disorders - Other (immune-mediated encephalitis)
- Increase in Risk Attribution:
  - Changed to Rare but Serious from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Peripheral motor neuropathy; Peripheral sensory neuropathy

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**UPDATES TO THE MODEL CONSENT:**

**What possible risks can I expect from taking part in this study?**

This section has updated risks and side effects related to ipilimumab used in Group 2 (and in Group 1 if cancer grows and patient is able to receive both drugs):

- Provided Further Clarification:
  - Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine is now reported as Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional, Some May be Serious).
  - Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body is now reported as Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare and Serious)
  - Swelling of the brain which may cause headache, blurred vision, stiff neck and/or confusion (under Rare) is now reported as Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck (under Rare and Serious) and is now under the “Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to” heading.

**A replacement protocol document and model consent form have been issued.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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ALLIANCE A091401

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*NCI-supplied agents: Nivolumab (NSC #748726, IND #126336); IND holder: CTEP  
Ipilimumab (NSC #732442, IND #126336), IND holder: CTEP*

**ClinicalTrials.gov Identifier: NCT02500797**

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**NRG** / NRG Oncology  
**SWOG** / SWOG

**Study Resources:**

<b>Expedited Adverse Event Reporting</b> <a href="http://eapps-ctep.nci.nih.gov/ctepaers/">http://eapps-ctep.nci.nih.gov/ctepaers/</a>	<b>Medidata Rave® iMedidata portal</b> <a href="https://login.imedidata.com">https://login.imedidata.com</a>
<b>OPEN (Oncology Patient Enrollment Network)</b> <a href="https://open.ctsu.org">https://open.ctsu.org</a>	<b>Biospecimen Management System</b> <a href="http://bioms.allianceforclinicaltrialsinoncology.org">http://bioms.allianceforclinicaltrialsinoncology.org</a>

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**Protocol-related questions may be directed as follows:**

<b>Questions</b>	<b>Contact (via email)</b>
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox <a href="mailto:regulatory@allianceNCTN.org">regulatory@allianceNCTN.org</a>
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox <a href="mailto:pharmacovigilance@alliancencn.org">pharmacovigilance@alliancencn.org</a>
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Ohio State

**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

<b><i>CONTACT INFORMATION</i></b>		
<b>For regulatory requirements:</b>	<b>For patient enrollments:</b>	<b>For study data submission:</b>
<p>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.</p> <p>Regulatory Submission Portal: (Sign in at <a href="http://www.ctsu.org">www.ctsu.org</a>, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYS_TEM/">https://www.ctsu.org/OPEN_SYS_TEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The most current version of the <b>study protocol and all supporting documents</b> must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <a href="https://www.ctsu.org">https://www.ctsu.org</a>. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.: Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p>		
<p><b><u>For clinical questions (i.e. patient eligibility or treatment-related)</u></b> contact the Study PI of the Lead Protocol Organization.</p>		
<p><b><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u></b> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><b>The CTSU Website is located at</b> <a href="https://www.ctsu.org">https://www.ctsu.org</a>.</p>		

**RANDOMIZED PHASE II STUDY OF NIVOLUMAB WITH OR WITHOUT IPILIMUMAB IN PATIENTS WITH METASTATIC OR UNRESECTABLE SARCOMA**

**Pre-Registration Eligibility Criteria (see [Section 3.2](#))**

Central pathology review submission (see [§ 3.2.1](#))

**Registration Eligibility Criteria (See [Section 3.3](#))**

Histologically confirmed bone or soft tissue sarcoma by central pathology review

Measureable disease as defined in [Section 11.0](#)

Locally advanced/unresectable or metastatic disease

≥ 1 prior systemic therapy for sarcoma

No prior therapy with ipilimumab or nivolumab or other agent targeting PD-1, PD-L1 or CTLA-4.

No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration. \*For GIST, tyrosine kinase inhibitor can be continued for up to 3 days prior to initiation of study treatment.

Resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

No history of the following:

- Active known or suspected autoimmune disease
- Symptomatic, untreated, or uncontrolled brain metastases
- Active autoimmune colitis
- Autoimmune panhypopituitarism
- Autoimmune adrenal insufficiency
- Known active hepatitis B or C ([see section 3.3.4](#) for definition)

No systemic treatment with corticosteroids or other immunosuppressive medications ≤ 14 days of registration.

Not pregnant and not nursing (see [Section 3.3.6](#))

Age ≥ 18 years

ECOG performance status 0 or 1

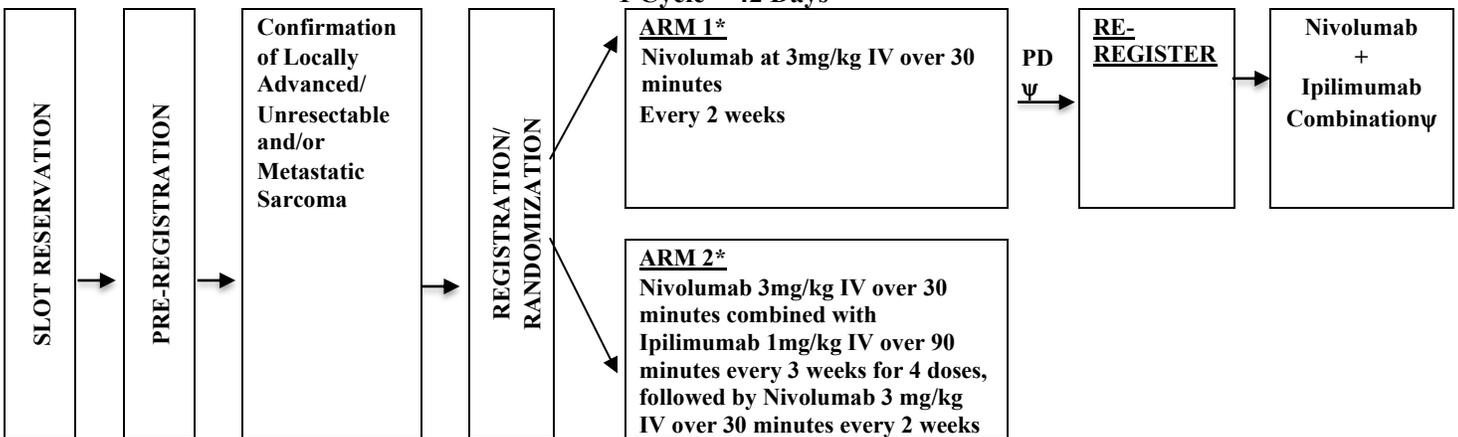
**Required Initial Laboratory Values**

Absolute neutrophil count (ANC)	≥ 1500/mm <sup>3</sup>
Platelet Count	≥ 100,000/mm <sup>3</sup>
Creatinine	< 1.5 x ULN
Calc. Creatinine Clearance (see Alliance website)	OR ≥ 45 mL/min*
Total Bilirubin	≤ 1.5 x ULN*
AST / ALT	≤ 3 x ULN
TSH	WNL*

\*See [section 3.3.9](#)

**Schema**

**1 Cycle = 42 Days**



\* During the first twelve weeks of therapy, patients who progress by imaging may be eligible to continue therapy. See [Section 7.1](#) for more information.

ψ Nivolumab 3mg/kg IV over 30 minutes combined with Ipilimumab 1mg/kg IV over 90 minutes every 3 weeks for 4 doses total followed by Nivolumab 3 mg/kg IV over 30 minutes every 2 weeks (See [Section 3.4](#), Section 4.6 and [Section 7.2](#) for further instructions).

Treatment is to continue for 108 weeks or until disease progression or unacceptable adverse events. Patients are followed for a maximum of three years post-randomization or until death, whichever comes first.

Please note that vaccinations should be administered prior to therapy (See [Section 8.1](#)).

**Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.**

## Table of Contents

<u>Section</u>	<u>Page</u>
<b>1.0 BACKGROUND.....</b>	<b>7</b>
1.1 Endpoints in Sarcoma Studies.....	7
1.2 Immunotherapy in Sarcoma.....	7
1.3 Immunologic Checkpoint Blockade.....	10
1.4 CTLA-4 blockade with ipilimumab.....	11
1.5 PD-1 blockade with nivolumab.....	11
1.6 Combination therapy utilizing ipilimumab and nivolumab.....	13
1.7 Rationale of 2 therapeutic arms of this trial.....	14
1.8 Rationale for crossover from single agent nivolumab to dual agent nivolumab/ipilimumab upon progression.....	14
1.9 Rationale for cohort expansion in GIST.....	15
1.10 Rationale for cohort expansion in UPS/MFH and LPS.....	16
1.11 Registration Quality of Life (QOL) Measurements.....	16
1.12 Impact of This Trial.....	16
<b>2.0 OBJECTIVES.....</b>	<b>17</b>
2.1 Primary objective.....	17
2.2 Secondary objectives.....	17
2.3 Correlative science objectives.....	17
2.4 Exploratory Phase II objectives (Crossover Treatment).....	17
<b>3.0 PATIENT SELECTION.....</b>	<b>18</b>
3.1 On-Study Guidelines.....	18
3.2 Pre-Registration Eligibility Criteria.....	19
3.3 Registration Eligibility Criteria.....	19
3.4 Re-registration Eligibility Criteria (For patients who crossover from arm 1 nivolumab alone to dual agent nivolumab and ipilimumab upon progression).....	21
<b>4.0 PATIENT REGISTRATION.....</b>	<b>23</b>
4.1 CTEP Investigator Registration Procedures.....	23
4.2 CTSU Site Registration Procedures.....	24
4.3 Patient Pre-registration Requirements (Step 0).....	25
4.4 Patient Registration Requirements (Step 1).....	26
4.5 Patient Pre-Registration/Registration/Randomization Procedures.....	26
4.6 Re-Registration (Step 2) at the time of progression.....	27
4.7 Registration to Correlative and Companion Studies.....	27
4.8 Grouping Factors.....	27
<b>5.0 STUDY CALENDAR.....</b>	<b>28</b>
<b>6.0 DATA AND SPECIMEN SUBMISSION.....</b>	<b>31</b>
6.1 Data collection and submission.....	31
6.2 Specimen collection and submission.....	32
<b>7.0 TREATMENT PLAN/INTERVENTION.....</b>	<b>38</b>
7.1 Treatment Decisions within the First Twelve Weeks of Therapy.....	38
7.2 Crossover to Dual Agent Nivolumab and Ipilimumab upon Progression on Arm 1 (single agent nivolumab).....	39
<b>8.0 DOSE AND TREATMENT MODIFICATIONS.....</b>	<b>41</b>
8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care.....	41

8.2	Dose Modifications .....	44
<b>9.0</b>	<b>ADVERSE EVENTS .....</b>	<b>49</b>
9.1	Routine adverse event reporting (solicited).....	49
9.2	Routine adverse event reporting (not solicited).....	49
9.3	Expedited Adverse event reporting (CTEP-AERS) .....	50
9.4	CAEPRs .....	53
<b>10.0</b>	<b>DRUG INFORMATION.....</b>	<b>62</b>
10.1	General Considerations .....	62
10.2	Nivolumab (BMS-936558, MDX-1106, ONO-4538 NSC #748726, IND #126336, IND holder: CTEP).....	62
10.3	Ipilimumab (BMS-734016, MDX-010, NSC#s 732442 and 720801, IND #126336, IND holder: CTEP).....	65
<b>11.0</b>	<b>MEASUREMENT OF EFFECT .....</b>	<b>69</b>
11.1	Schedule of Evaluations: .....	69
11.2	Definitions of Measurable and Non-Measurable Disease .....	69
11.3	Guidelines for Evaluation of Measurable Disease .....	70
11.4	Measurement of Treatment/Intervention Effect .....	71
11.5	Definitions of analysis variables .....	74
<b>12.0</b>	<b>END OF TREATMENT/INTERVENTION .....</b>	<b>75</b>
12.1	Duration of Treatment .....	75
12.2	Crossover.....	75
12.3	Managing ineligible patients and registered patients who never receive protocol intervention... 75	75
12.4	Extraordinary Medical Circumstances .....	76
<b>13.0</b>	<b>STATISTICAL CONSIDERATIONS .....</b>	<b>77</b>
13.1	Study Overview .....	77
13.2	Primary Endpoint .....	77
13.3	Study Design .....	78
13.4	Secondary Endpoints.....	79
13.5	Exploratory and Correlative Endpoints .....	80
13.6	Total Sample Size, Accrual Duration, and Anticipated time to study completion.....	80
13.7	AE Stopping Rule.....	81
13.8	Accrual Monitoring Stopping Rule .....	82
13.9	Primary Endpoint Completion Time Estimation (For clinicaltrials.gov reporting) .....	82
13.10	Descriptive Factors.....	82
13.11	Inclusion of Women and Minorities.....	82
<b>14.0</b>	<b>CORRELATIVE AND COMPANION STUDIES .....</b>	<b>83</b>
14.1	Mandatory studies and optional Correlative Science (Alliance A091401-ST1) .....	84
<b>15.0</b>	<b>GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING.....</b>	<b>89</b>
<b>16.0</b>	<b>REFERENCES .....</b>	<b>90</b>
<b>APPENDIX I</b>	<b>REGISTRATION FATIGUE/UNISCALE ASSESSMENTS.....</b>	<b>93</b>
<b>APPENDIX II</b>	<b>CRADA .....</b>	<b>94</b>
<b>APPENDIX III</b>	<b>TOXICITY ALGORITHMS .....</b>	<b>96</b>
<b>APPENDIX IV</b>	<b>DEFINITION OF ACTIVE AUTOIMMUNE DISEASE .....</b>	<b>103</b>
<b>APPENDIX V</b>	<b>MANAGEMENT OF INFUSION REACTIONS .....</b>	<b>104</b>

## 1.0 BACKGROUND

Sarcomas are heterogeneous malignant tumors of mesenchymal origin characterized by more than 100 distinct subtypes. Approximately 13,000 cases of soft tissue and bone are diagnosed annually in the US. Surgery, often with adjuvant radiation for larger tumors, is the mainstay of treatment.[1] Perioperative chemotherapy has proven efficacy only in specific chemosensitive subtypes such as rhabdomyosarcoma, osteosarcoma and Ewing sarcoma.[1] Despite primary combined modality therapy, between 25-50% of patients develop recurrent and/or metastatic disease, dependent upon initial stage and subtype.[2, 3] Complete responses to chemotherapy for recurrent or metastatic sarcoma are rare and median survival in the metastatic setting is 10-15 months.[4, 5] Standard cytotoxic chemotherapy agents such as doxorubicin, ifosfamide and dacarbazine have response rates 10-30%.[6] The development of novel and effective therapies in sarcoma patient populations is urgently needed.

### 1.1 Endpoints in Sarcoma Studies

Historical data show that the prognosis for advanced sarcoma patients who have failed at least one prior therapy is poor, with 90% experiencing disease progression within 6 months (i.e., the 6-month progression-free survival is 10%).[7] Thus, we consider the prolonged progression-free survival in this patient population to be a meaningful result.

Progression-free survival (PFS) is used increasingly as a metric for comparison of chemotherapeutic agents in sarcomas, given that response rates are relatively low, at least in part due to the biology of chemotherapy responses of sarcomas, which die more frequently by senescence than by apoptosis. The best available data regarding PFS comes from EORTC databases.[7] In this analysis, PFS was estimated in both previously treated and previously untreated patients, based on analysis of 12 clinical trials of different agents in which in only two cases (ifosfamide and dacarbazine) was there a significant response rate. Comparison was made between responses to these two agents vs. inactive agents (all others examined in these studies). Response assessment was made by WHO criteria for these studies performed reported between 1991 and 1999. A total of 1154 patients were examined who had not received prior therapy, while 146 cases with prior anthracyclines who then received ifosfamide or dacarbazine constituted the responding cohort. 234 patients receiving what were termed inactive agents/regimens were used as a comparator.[7] For patients who had received prior therapy, PFS was better with active drugs than inactive drugs in a multivariate analysis. Performance status was of borderline significance ( $p=0.08$ ). For previously treated patients, PFS was 21% at 3 months for inactive drugs/regimens, and 39% for active drugs; 6 month PFS was 8% with inactive regimens, and 14% for active regimens. In patients who had not received prior chemotherapy, 3 month PFS varied from 44-77%, depending on histology, and 6 month PFS varied between 30% and 56%.

### 1.2 Immunotherapy in Sarcoma

Immunotherapeutic strategies may be a promising approach to this disease. The role of the immune system as a mechanism of cancer therapy was in fact first observed in a sarcoma patients. Dating back to 1866, Wilhelm Busch in Germany observed tumor regressions in patients with sarcoma after postoperative wound infections.[8] Coley described a dramatic response in a patient with small cell sarcoma after an erysipelas infection, suggesting that the body's response to infection also had potential anti-tumor effects.[9] The observation that the development of sarcoma is more common in patients that are immunosuppressed also supports the relevance of the immune surveillance in this disease.[10] Perhaps the best example of this is the development of in immunosuppressed patients.[11] The development of sarcomas have also been described in allograft transplant recipients. Thus, the immune system is critical

in sarcoma control and progression, and appropriate modulation of the immune system may provide an effective therapeutic option for this disease.

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

The prognostic significance of lymphocyte infiltration of soft tissue sarcomas has been investigated.[12] A tissue microarray from 249 patients with STS was constructed evaluating CD3+, CD4+, CD8+ and CD20+ lymphocytes in the tumors. In a multivariate analysis, CD20+ infiltration was found to be an independent positive prognostic factor in patients that underwent surgical resection and had wide resection margins, (HR=5.5, CI 95% 1.6-18.6, p=0.006.)[12] This suggests the lymphocytes are present in sarcomas and may play a role in the patient outcomes. Therefore, manipulating the immune system in sarcoma may prove to be an effective therapeutic intervention in these patients.

#### **PDL-1 Expression in Sarcoma Cell Lines**

In vitro models using sarcoma cell lines have documented very high PDL1 expression at baseline by Western blot (Figure 1) and by flow cytometry (Figure 1) that is also induced by interferon. Expression is noted in nearly 65% of the cell lines including synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumors, desmoplastic small round cell, osteosarcoma and chondrosarcoma.

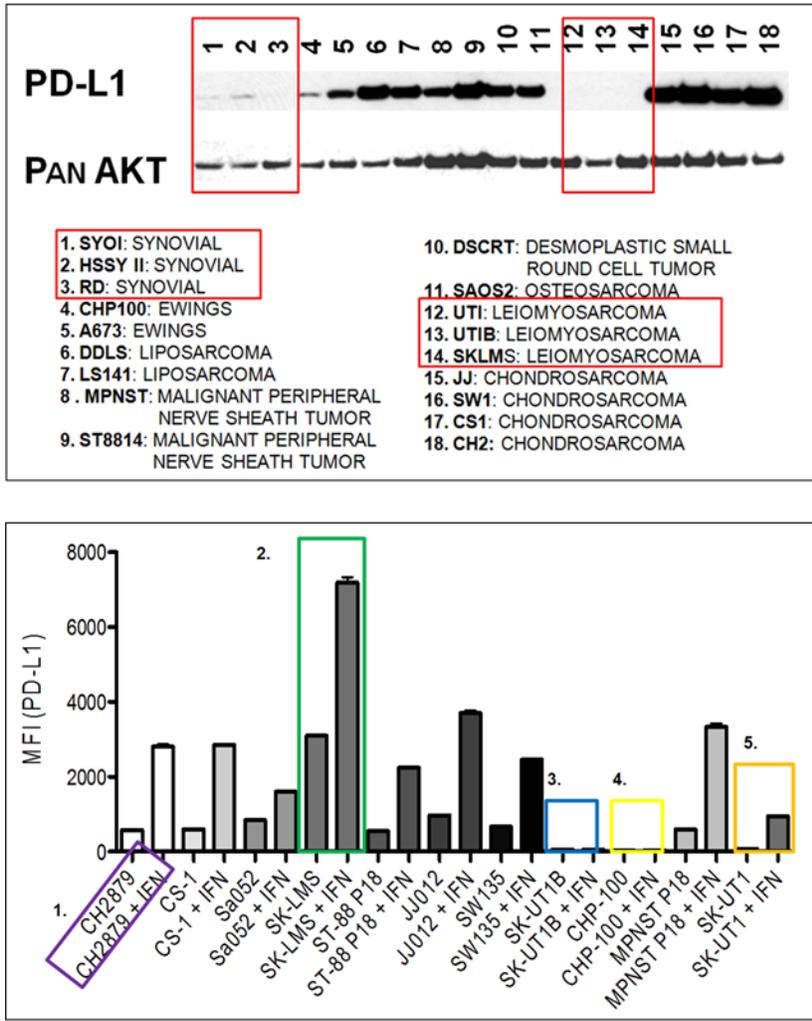


Figure 1

**A. Western Blot**

(18 cell lines)  
 • Expression was noted in all tested cell lines except synovial sarcoma and leiomyosarcoma (as indicated by red box).

**B. Flow Cytometry**

(11 cell lines; SYOI, HSSYII, RD, A673, MPNST, DSCRT, CH2: excluded in analysis)

1. CH2879 tested by flow cytometry, but not by western blot.
2. Expression in SK-LMS is absent by western blot data, but present and inducible with interferon.
3. SK-UT1B negative by flow cytometry and not inducible with interferon.
4. CHP-100 negative by flow cytometry and not inducible with interferon but positive with western blot.
5. SK-UT1 negative by flow cytometry but inducible with interferon.

\* Different antibodies were used for each technique; this contributed to these noted discrepancies.

**PDL-1 Expression in Sarcoma Tumor Specimens**

PDL-1 expression was evaluated in 50 sarcoma tumor specimens of various subtypes using immunohistochemistry with the use of a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8) and an automated assay developed by Dako. Greater than 1% PDL-1 expression was identified in 6/50 (12%) of samples (Table 1). There was evidence of macrophage and lymphocyte infiltration in the tumor, outside of the tumor, and both.

Median age 46 years (range, 22 - 76), 66% male. Disease status: 70% primary disease/locally recurrent, 26% metastatic and 4% unknown. Tumor, lymphocyte and macrophage PD-L1 expression was noted in 12%, 30% and 58%, respectively. Lymphocyte and macrophage infiltration was present in 98% and 90%, respectively. (Table 1)

### Immunohistochemistry

Immunohistochemical staining for PD-L1 (DAKO, Carpinteria, CA) will be performed on 5 µm thick sections obtained from formalin-fixed paraffin embedded tissue of the selected cases. PD-L1 positivity was defined as >1% of tumor cells (minimum of 100 evaluable cells) demonstrating plasma membrane staining. Macrophage and lymphocyte PD-L1 status was determined qualitatively. Positive macrophage or lymphocyte PD-L1 expression inside and/or outside of the tumor expression was defined.

Immunohistochemical staining for PD1 (mouse clone NAT antibody, LOT#GR81330-2 Abcam Cambridge, MA or equivalent).

Table 1: PD-L1 expression				
Histology	n	% Tumor PD-L1 +	% Lymphocyte PD-L1 +	% Macrophage PD-L1 +
Angiosarcoma	3	0	100	100
GIST	14	27	100	100
Leiomyosarcoma	4	0	0	25
Liposarcoma	5	0	20	60
Synovial Sarcoma	3	0	33	0
Radiation associated pleomorphic sarcoma	1	100	100	100
Other	20	5	10	70
Overall	50	12	30	58

#### PD-L1 expression is not an established biomarker predictive of response

The significance of PD-L1 expression as a biomarker of response to checkpoint blockade with PD-1 inhibitors remains a controversial topic. PD-L1 expression remains a dynamic marker, that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute to varied PD-L1 expression.(30) Based on the initial phase I clinical data of the combination of ipilimumab and nivolumab in melanoma patients, patients with PD-L1 expression may be more likely to respond, however, lack of expression did not exclude responses. (29) These data suggest that either PD-L1 expression may change as a result of therapy with checkpoint blockade such as ipilimumab or nivolumab. Therefore, it remains pertinent to explore this biomarker as an integral part of the study.

### 1.3 Immunologic Checkpoint Blockade

T cell activation requires dual signaling.[13, 14] The binding of the T cell receptor to antigens presented by antigen presenting cells via major histocompatibility complex I and II is the first required signal in T cell activation. Subsequently, the second signal is generated when the B7 ligand bind to CD28 which is a co-stimulatory receptor. This signaling leads to T cell proliferation, cytokine release and upregulation of the immune response. As a result, CTLA-4 is upregulated and competes with B7 for CD28 binding. Ultimately, CTLA4 has higher affinity for the CD28 receptor and the T cell response is down-regulated. CTLA-4 is a negative regulator of T cell responses that prevents autoimmunity and allows tolerance to self antigens.[13]

PD-1 is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS and BTLA.[15] PD-1 is expressed on activated T cells, B cells and myeloid cells.[16] There are 2 ligands, PD-L1 and PD-L2 that are specific for PD-1. Once they bind to PD-1, down-regulation of T-cell activation occurs.[17, 18] When the PD-1 ligand binds to the receptor, T cell activation is blocked. If this interaction is interrupted, the checkpoint is turned off and antitumor T-cell activation maybe enhanced. I

## 1.4 CTLA-4 blockade with ipilimumab

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4, Yervoy™) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells (Ipilimumab Investigator Brochure, 2014). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and inhibits its interaction with ligands on antigen-presenting cells (APCs). The proposed mechanism of action for ipilimumab's effects in subjects with melanoma is indirect, possibly through T-cell potentiation and mediation of antitumor immune responses.

Ipilimumab has been FDA approved for the treatment of melanoma, demonstrating an improvement in overall survival.[19] The response rate of ipilimumab is about 10%-20%.[20] Since clinical responses can be delayed, many patients do not demonstrate disease regression for until weeks after therapy is complete and some patients can have initial progressive disease and subsequent disease stabilization. Therefore, one must consider inclusion of alternate endpoints such as improvement in immune-related progression-free survival as well as overall survival. A set of novel response criteria termed immune-related response criteria (irRC) have been developed to capture these unique response patterns.[21] With the irRC, progressive disease is defined as total disease growth up to 25% from baseline or total disease burden (new lesions + target) greater than 25%. In addition, using this therapy earlier in the metastatic setting, when patients are asymptomatic and perhaps have less disease burden may be more effective. This will allow for sufficient time to see a potential immune response.

### Ipilimumab in sarcoma

In a small phase II study, patients with synovial sarcoma were treated with ipilimumab 3mg/kg every 3 weeks and re-staged after 3 cycles.[22] Serum and peripheral blood was collected before and during therapy to assess NY-ESO-1 specific immunity. The primary endpoint of the study was RECIST 1.0 response rate. A response rate of at least 25% would be considered worthy of activity and further evaluation. Secondary endpoints included determination of the clinical benefit rate (CR + PR+ SD) and evaluation of NY-ESO-1 specific immunity. Six patients received 1 to 3 cycles of ipilimumab. Four patients completed 3 doses of ipilimumab, while 2 patients each received 1 and 2 doses due to clinical or radiologic progression. There were no documented responses, and the time to progression ranged from 0.47 months- 2.1 months. There was no evidence of serologic or delayed type hypersensitivity to NY-ESO-1.

## 1.5 PD-1 blockade with nivolumab

### PD-1 and PD-L1

Programmed death 1 (PD-1) receptor is another promising potential immunological target. PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that include Ig super family member CD28, CTLA-4, inducible costimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2014). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the

activated T-cell immune response through SHP-1 phosphatase PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment.[23] Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma[24], renal[25-27], esophageal[28], gastric[29], ovarian[30], pancreatic[31], lung[32], and other cancers (Investigator Brochure, 2014).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

### **Nivolumab**

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, 2014). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype.

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 2014).

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses.[33] Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively.[34] In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting  $\geq 1$  year.[35]

In a study that enrolled and treated 296 patients with nivolumab, an antibody to PD-1, response rates were 18%, 28% and 27% in patients with non-small cell lung cancer, melanoma and renal cell carcinoma, respectively.[36] PD-L1 expression has been demonstrated in many tumors and has correlated with decreased immune system function and worse prognosis.[25, 28, 37-39] Further, there was initial suggestion that PD-L1 expression may correlate with clinical activity of PD-1 blockade. An immunohistochemistry assay was used to measure PD-L1 expression in 42 patients treated with nivolumab. There were 18 patients that lacked expression and all of

them did not have any evidence of benefit to the drug. In a subgroup of patients with melanoma, the positive predictive value was 40%.[36]

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet.[40] No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

A maximum tolerated dose (MTD) of nivolumab was not defined.[36] Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group[41], grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these events.

## 1.6 Combination therapy utilizing ipilimumab and nivolumab

While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for ipilimumab and nivolumab. Preclinical data support the combinations of nivolumab and ipilimumab.[42]

The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients.[41] In the phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen).[41] The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count.[41] With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1-positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1-positive tumor samples (6 of 13 patients) or PD-L1-negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1-positive tumor samples (4 of 8 patients) than among patients with PD-L1-negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon- $\gamma$  (IFN- $\gamma$ ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

For RCC results have been reported.[43] Pts were randomized to nivolumab 3mg/kg + ipilimumab 1mg/kg (n=21) and nivolumab 1mg/kg + ipilimumab 3mg/kg (n=23). Most pts (n=34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). Objective response rate (ORR) was 29% (nivolumab 3mg/kg + ipilimumab 1mg/kg) and 39% (nivolumab 1mg/kg+ ipilimumab 3mg/kg.) Duration of response was 4.1 to 22.1 weeks (all 6 responses ongoing) in

nivolumab 3mg/kg + ipilimumab 1mg/kg, and 6.1 yo 18.3 weeks (8/9 responses ongoing) in nivolumab 1mg/kg+ ipilimumab 3mg/kg. Responses occurred by first tumor assessment at week 6 in 67% of responding patients in both patient cohorts. Stable disease was seen in 7 (33%) patients (nivolumab 3mg/kg + ipilimumab 1mg/kg) and 9 (39%) patients (nivolumab 1mg/kg + ipilimumab 3mg/kg). Treatment-related adverse events (AEs) were seen in 89% of patients with 16% discontinuation due to any-grade related AEs. Grade 3–4 related AEs 43%, most commonly ↑ lipase (16%, n=7), ↑ ALT (11%, n=5), diarrhea (9%, n=4), colitis (5%, n=2), ↑ amylase (5%, n=2). No grade 3–4 pneumonitis was seen. Based on the above background trials, the combination is being evaluated in other disease settings typically with 3mg/kg nivolumab and 1mg/kg ipilimumab q 3 weeks during induction, for 4 doses. This is the induction dosing we have chosen for the combination arm of the trial.

### **1.7 Rationale of 2 therapeutic arms of this trial**

There is interest in conducting 2 concurrent phase II studies exploring single agent nivolumab as well as the combination of nivolumab and ipilimumab. In metastatic melanoma, published data has demonstrated promising results with single agent nivolumab but the combination has been even more promising.

By conducting this study single agent efficacy of nivolumab will be determined. In addition, it will be explored if the combination arm leads to higher responses. This will be important to plan future clinical studies.

### **1.8 Rationale for crossover from single agent nivolumab to dual agent nivolumab/ipilimumab upon progression**

Recently published data has demonstrated superiority of responses with combination therapy with nivolumab and ipilimumab [49-52]. This data has shown near doubling of overall response rates across multiple diseases including, but not limited to melanoma, non-small cell lung cancer and renal cell carcinoma.

Given the high overall activity, the combination of nivolumab and ipilimumab was FDA approved for the treatment of metastatic melanoma. It was shown that the complete response rate with the combination was 17% versus none with nivolumab monotherapy for patients with melanoma. Further, ORR with the combination was found to be independent of PD-L1 status. In PD-L1–positive and –negative tumors, respectively, ORR was 58% and 55% with nivolumab/ipilimumab. More recently, frontline combination therapy with nivolumab and ipilimumab was demonstrated to be active in patients with non-small cell lung cancer receiving one of four dosing regimens of nivolumab and ipilimumab. It was noted that the ORR ranged from 13% to 39%, regardless of PD-L1 status. Further, in renal cell carcinoma, single agent nivolumab has demonstrated an ORR in 20% of patients while the combination of nivolumab and ipilimumab has demonstrated responses ranging from 43-48%.

Given the now known promise and overall higher degree of activity with the combination of nivolumab and ipilimumab, regardless of PD-L1 status in many other disease types- there is now rationale to allow a cross-over to dual therapy, for patients with locally advanced/metastatic sarcoma that have progressed on single agent nivolumab. Overall the 2-drug regimen appears to be more effective therapy than single agent, and while there is limited data in sarcoma, performing this crossover will provide access to dual agent therapy without affecting the integrity of the primary endpoint of the study and scientific design. Many of these patients will be excluded from future clinical trials with checkpoint blockade, as most trials will exclude patients with prior exposure to nivolumab. Also, sarcoma currently has minimal FDA approved

therapies and clinical trials are a mainstay of treatment. Therefore, with Update #04 of the protocol, the option of allowing re-registration and crossover to dual agent therapy, upon progression on single agent nivolumab, was added to the protocol.

## 1.9 Rationale for cohort expansion in GIST

GIST are the most common sarcomas of the digestive tract and are thought to arise from or share a common ancestor with the interstitial cells of Cajal, the autonomic pacemaker cells of the gut that coordinate peristalsis. Approximately 4000 to 6000 new cases of GIST are diagnosed in the US each year.<sup>1,2</sup> Between 75% and 80% of these tumors contain activating mutations of KIT or PDGFR-alpha,<sup>3,4</sup> providing oncogenic signaling and driving tumor growth.<sup>5</sup> Given this, multiple small molecule tyrosine kinase inhibitors (TKI) against KIT and PDGFRA, such as imatinib, sunitinib, sorafenib and dasatinib, have been evaluated for the treatment of this disease.

Advanced GIST is refractory to conventional chemotherapy or radiotherapy, but multiple TKIs have been shown to have antitumor activity in this disease. Imatinib mesylate, a multi-targeted TKI with activity against PDGFR, KIT, BCR-ABL, ABL and LCK, has become the first line standard of care in advanced GIST achieving disease control in 70% to 85% of patients, with a median progression free survival of 20 to 24 months.<sup>6,7</sup> Although treatment with imatinib has greatly increased survival and quality of life for patients with advanced GIST, a subset of patients acquire kinase mutations in KIT or PDGFR-alpha that interfere with imatinib activity and ultimately lead to imatinib resistance.<sup>8-10</sup>

At time of progression, the currently accepted treatment strategies include dose escalation of imatinib<sup>11</sup> or transition to treatment with sunitinib.<sup>12</sup> Sunitinib is a multi-targeted TKI with a kinase spectrum including VEGF as well as PDGFR and KIT, among others. In an international phase III trial of imatinib refractory patients, sunitinib showed a median time to tumor progression of 27.3 weeks compared to 6.4 weeks in those on placebo.<sup>13</sup> Based on this and other data, sunitinib has been FDA approved for the treatment of imatinib-refractory or intolerant advanced GIST.

Although treatment of GIST with tyrosine kinase inhibitors results in demonstrated clinical benefit, this efficacy is not indefinite and treatment with KIT inhibition does not result in the cure of patients with advanced disease. Alternate options are necessary to improve outcomes for patients with TKI resistant GIST.

An attractive potential therapy for GIST is immunotherapy. There is pre-clinical evidence of benefit from immunotherapy in GIST. A study of 50 sarcoma patients treated at Memorial Sloan-Kettering Cancer Center consented to a tissue procurement protocol and collected correlative clinical information. Immunohistochemistry staining of tumor specimens was performed with the use of a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8) and an automated assay developed by Dako. Findings were the following: there was >1% PDL-1 expression in 6/50 (12%) of samples that included all sarcoma subtypes. Positive PD-L1 expression was noted in 27% of GIST samples. Of all tested histologies, the highest level of expression was noted in GIST.

The high PD-L1 expression noted in GIST tumor samples prompted further pre-clinical work in this disease. In collaboration with the DeMatteo lab, PD-L1 expression in tumor samples was re-explored as well as the efficacy of PD-1 blockade and sunitinib in mouse models. Over half of resistant GIST specimens contain intratumoral CD8 T cells that express substantial levels of PD-L1.

GIST is a malignancy with a marked difference in pathogenesis and treatment, compared to other sarcomas. The standard cytotoxic agents that are utilized in sarcoma are ineffective in GIST, and tyrosine kinase inhibitors are the standard of care. As described above, pre-clinical data suggests that PD-L1 expression is much higher in GIST compared to other sarcomas,

therefore, there is rationale to evaluate these agents in GIST, as separate cohorts given the overall different biology.

### **1.10 Rationale for cohort expansion in UPS/MFH and LPS**

Recent data from ASCO 2016 by Hussein Tawbi et al. noted efficacy of pembrolizumab in selected sarcomas. In a trial that enrolled 80 sarcoma patients, 40 bone (Ewing's, Osteosarcoma, Chondrosarcoma) and 40 soft tissue (leiomyosarcoma [LMS], undifferentiated pleomorphic sarcoma [UPS]/malignant fibrous histiocytoma [MFH], dedifferentiated/pleomorphic liposarcoma [LPS], synovial sarcoma), the overall response rate was 19.5%. There were higher responses in the MFH/UPS and LPS subtypes, tumors thought to be characterized by high mutational burden and high tumor infiltrating lymphocytes. Given the promising activity in these subtypes there is rationale to expand the trial in these 2 histologies.

### **1.11 Registration Quality of Life (QOL) Measurements**

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. It will take approximately one minute to complete this measure. [44]

### **1.12 Impact of This Trial**

Sarcomas represent a heterogeneous group of neoplasms with a limited number of therapeutic options in metastatic disease. There is indirect evidence from preclinical analysis of markers such as PDL-1 and characterization of immune infiltrates in human tissue samples that certain sarcomas may benefit from immune checkpoint blockade. This trial will represent one of the first Phase II studies of immune checkpoint blockade in sarcomas, and the first to combine CTLA-4 and PD-1 blockade in sarcoma. Planned correlates will investigate retrospective biomarkers that may predict which patients will respond to these therapies.

## **2.0 OBJECTIVES**

As of Update #06, the study objectives will be evaluated within the initial cohort of patients enrolled, as well as within 3 cohorts of patients defined by the following histologic subtypes: LPS, UPS/MFH, and GIST.

### **2.1 Primary objective**

To evaluate the confirmed response rate of single agent nivolumab and dual agent nivolumab plus ipilimumab in patients with locally advanced/unresectable or metastatic soft tissue sarcoma.

### **2.2 Secondary objectives**

**2.2.1** To evaluate adverse event rates (NCI CTCAE v4.0) within each treatment arm.

**2.2.2** To evaluate duration of response, clinical benefit rate, time to progression, progression-free survival, and overall survival within each treatment arm.

### **2.3 Correlative science objectives**

**2.3.1** To potentially detect an early signal of confirmed response rate within a histologically defined patient cohort.

**2.3.2** To assess the potential association between PD-L1 expression (by IHC) and clinical outcome, within each treatment.

**2.3.3** To evaluate associations between selected biomarker measured in serial peripheral blood and with clinical efficacy, within each treatment.

**2.3.4** To evaluate the association between selected biomarker measured in tumor tissue with clinical efficacy, within each treatment.

**2.3.5** To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy within each treatment.

### **2.4 Exploratory Phase II objectives (Crossover Treatment)**

**2.4.1** To evaluate secondary endpoints within patients crossing over to dual agent nivolumab plus ipilimumab after experiencing progressive disease while receiving single agent nivolumab.

**2.4.2** To evaluate correlative science objectives endpoints within patients crossing over to dual agent nivolumab plus ipilimumab after experiencing progressive disease while receiving single agent nivolumab.

### 3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the [Study Resources](#) page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

#### 3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol, and the following patients will not be enrolled:

- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for  $\geq 1$  year.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and continue for 5 months (women) and 7 months (men) after the last dose of study drugs, even if oral contraceptives are also used, due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated should be assessed as per the study calendar (see Section 5.0) for appropriateness for participation on this trial.

## 3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

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

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

### 3.2.1 Central pathology review submission

Patients must have a FFPE tumor block OR 1 representative H&E and 20 unstained sarcoma tissue slides available for submission for central pathology review. This review is mandatory prior to registration to confirm eligibility. See [Section 6.2](#) for details on slide/block submission.

## 3.3 Registration Eligibility Criteria

### 3.3.1 Documentation of Disease

Histologic Documentation:

**Prior to Update #06:** Patients must have histologically confirmed bone or soft tissue sarcoma by central pathology review.

**Effective with Update #06:** Patients must have histologically confirmed LPS (only dedifferentiated and pleomorphic. Well differentiated not eligible), UPS/MFH, or GIST.

### 3.3.2 Disease Status

Measurable disease as defined in [Section 11.0](#).

Locally advanced/unresectable or metastatic disease.

### 3.3.3 Prior Treatment

- $\geq 1$  prior systemic therapy for sarcoma, including adjuvant systemic therapy.
- No prior therapy with ipilimumab or nivolumab, or any agent targeting PD-1, PD-L1 or CTLA-4.
- No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation  $\leq 28$  days before study registration. No treatment with nitrosourea or mitomycin  $\leq 42$  days before study registration. For GIST, tyrosine kinase inhibitor can be continued for up to 3 days prior to initiation of study treatment.
- Patients should have resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

### 3.3.4 No history of the following:

- Active known or suspected autoimmune disease. [See Appendix IV](#) for details.
- Patients with HIV are eligible if the lymphocytes  $> 350$  CD4+ cells and no detectable viral load
- Symptomatic, untreated, or uncontrolled brain metastases present.

- Active autoimmune colitis
- Autoimmune panhypopituitarism
- Autoimmune adrenal insufficiency
- Known active hepatitis B or C

**Hepatitis B Can be defined as:**

1. HBsAg > 6 months
2. Serum HBV DNA 20,000 IU/ml (105copies/ml), lower values 2,000-20,000 IU/ml (104-105 copies/ml) are often seen in HBeAg-negative chronic hepatitis B
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

**Hepatitis C can be defined as:**

1. Hepatitis C AB positive
  2. Presence of HCV RNA
- Known active pulmonary disease with hypoxia defined as
    1. Oxygen saturation < 85% on room air or
    2. Oxygen saturation <88% despite supplemental oxygen

\_\_\_ **3.3.5 Concomitant Medications:**

No systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of registration.

\_\_\_ **3.3.6 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done  $\leq 7$  days prior to registration is required.

\_\_\_ **3.3.7 Age  $\geq 18$  years**

\_\_\_ **3.3.8 ECOG Performance Status 0 or 1.**

\_\_\_ **3.3.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	$\geq 1,500/\text{mm}^3$
Platelet Count	$\geq 100,000/\text{mm}^3$
Creatinine	$\leq 1.5 \times$ upper limit of normal (ULN) <b>OR</b>
Calc. Creatinine Clearance	$> 45 \text{ mL/min}^*$
Total Bilirubin	$\leq 1.5 \times$ upper limit of normal (ULN)**
AST / ALT	$\leq 3 \times$ upper limit of normal (ULN)
TSH	WNL***

\* Using the lean body mass formula only (Modified Cockcroft and Gault; Shargel and Yu 1985)

\*\* In absence of Gilbert disease (Total Bilirubin  $\leq 3 \times$  ULN with Gilbert). Also, if hyperbilirubinemia is clearly attributed to liver metastases total bilirubin  $\leq 3 \times$  ULN is permitted

\*\*\* Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

### 3.4 Re-registration Eligibility Criteria (For patients who crossover from arm 1 nivolumab alone to dual agent nivolumab and ipilimumab upon progression)

#### 3.4.1 Disease Status

- Measurable disease as defined in [Section 11.0](#).
- Locally advanced/unresectable or metastatic disease.
- Patient MUST have had progressive disease (radiographic or clinical) while on arm 1 single agent nivolumab while registered to A091401.

#### 3.4.2 Prior Treatment

- Patients removed from any immunotherapy for reasons other than progressive disease, including arm 1 single agent nivolumab of A091401, are NOT eligible for re-registration
- Patients must have completed a minimum of 10 weeks of single agent nivolumab on arm 1 of A091401 to be eligible for re-registration
- Patients must have completed study drug on arm 1 of A091401 (i.e., last dose of nivolumab)  $\leq$  12 months of re-registration to crossover dual agent therapy
- No treatment with immunotherapy  $\leq$  21 days before re-registration. No treatment with biologic therapy, chemotherapy, investigational agent for malignancy, or radiation  $\leq$  28 days before re-registration. No treatment with nitrosourea or mitomycin  $\leq$  42 days before re-registration.
- Patients should have resolution of any toxic effects of prior therapy (except fatigue and alopecia) to NCI CTCAE, Version 4.0, grade 1 or less, including immune toxicity.

#### 3.4.3 Concomitant Medications:

No systemic treatment with either corticosteroids ( $>$  10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of re-registration.

#### 3.4.4 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done  $\leq$  7 days prior to re-registration is required.

#### 3.4.5 ECOG Performance Status 0 or 1.

#### 3.4.6 Required Laboratory Values:

Absolute Neutrophil Count (ANC)	$\geq$ 1,500/mm <sup>3</sup>
Platelet Count	$\geq$ 100,000/mm <sup>3</sup>
Creatinine	$\leq$ 1.5 x upper limit of normal (ULN) <b>OR</b>
Calc. Creatinine Clearance	$>$ 45 mL/min*
Total Bilirubin	$\leq$ 1.5 x upper limit of normal (ULN)**
AST / ALT	$\leq$ 3 x upper limit of normal (ULN)
TSH	WNL***

- \* Using the lean body mass formula only (Modified Cockcroft and Gault; Shargel and Yu 1985)

- \*\* In absence of Gilbert disease (Total Bilirubin  $\leq 3 \times$  ULN with Gilbert). Also, if hyperbilirubinemia is clearly attributed to liver metastases total bilirubin  $\leq 3 \times$  ULN is permitted
- \*\*\* Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

## 4.0 PATIENT REGISTRATION

### 4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iam>). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
HSP/GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR **Help Desk** by email at [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov).

## 4.2 CTSU Site Registration Procedures

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

### IRB Approval:

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

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

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

### 4.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A091401 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to <https://www.ctsuo.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # A091401
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided.

### 4.2.2 Requirements for A091401 Site Registration

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

#### 4.2.3 Submitting Regulatory Documents

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

Regulatory Submission Portal: [www.cts.org](http://www.cts.org) (members' area) → Regulatory Tab → Regulatory Submission.

When applicable, original documents should be mailed to:

CTSU Regulatory Office  
1818 Market Street, Suite 3000  
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

#### 4.2.4 Checking Your Site's Registration Status

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

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

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

### 4.3 Patient Pre-registration Requirements (Step 0)

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Slot reservation:** As of Update #06, patient enrollment will be facilitated using the Slot Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the correct cohort is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to consent and pre-register the patient. Once a patient is pre-registered, specimens should be submitted for central pathology review. There will be no renewal of slots for this protocol. Therefore, pre-registration must be completed within 7 calendar days of slot reservation.
- **Central pathology:** Patients who meet the pre-registration eligibility criteria will be pre-registered using the OPEN registration system (see [Section 4.5](#)) in order to submit specimens for central pathology review. Once a patient is pre-registered, the archival FFPE tumor block OR 1 representative H&E and 20 unstained sarcoma tissue slides (thickness of 4-5 microns) from diagnostic biopsy should be sent to the Alliance Biorepository at Ohio State (OSU) along with a completed "Central Pathology Review Form", per [Section 6.2.3](#). **Failure to submit this form with the specimens will delay turnaround time for central**

**pathology review.** The specimen will be centrally reviewed to confirm the patient meets the pathology criteria.

- **For all Investigators:** Patients should be encouraged to verify that their medical insurance will cover the costs associated with the frequency of the scanning schedule (see Section 5.0, Study Calendar).

#### 4.4 Patient Registration Requirements (Step 1)

- **Confirmation of eligibility by central pathology review:** Sites will be notified via e-mail within 10 business days of receipt, whether or not the patient is eligible based on the central pathology review. The results section of the “Central Pathology Review Form” will be completed by the pathologist, scanned and sent via e-mail to the Responsible CRA listed on the form. The form will indicate whether or not the patient is eligible, and if a discrepancy was found in central vs. local pathology review. If the central review disagrees with local review, then the following may occur:
  - Complete discordance: the patient is ineligible for the trial. The treating physician should inform the patient and determine next steps.
  - Partial discordance: the patient is eligible (as this trial allows all sarcoma subtypes), but the treating physician at the site may determine whether not they would like to register the patient to the trial. The patient should be informed of the discordance.

After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at [random01@mayo.edu](mailto:random01@mayo.edu) in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration and Randomization Eligibility Criteria have been met, the patient can be registered using the OPEN system per [Section 4.5](#). Registration must occur within 40 days of specimen submission. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance Patient Registration office at [random01@mayo.edu](mailto:random01@mayo.edu) or 507-284-4130 if registration problems occur.

#### 4.5 Patient Pre-Registration/Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < [https://ctepcore.nci.nih.gov/iam\\_>](https://ctepcore.nci.nih.gov/iam_>)) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>. To assign an IVR or NPVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- As of Update #06, tumor histology (local diagnosis) is one of the following:
  1. LPS
  2. UPS/MFH
  3. GIST

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

#### 4.6 Re-Registration (Step 2) at the time of progression

Upon confirmation of progression, patients who were initially assigned to nivolumab alone (Arm 1) will be allowed to cross over to the dual agent arm (Arm 2).

##### Re-registration procedures:

- Call (507-284-4130) or email ([random01@mayo.edu](mailto:random01@mayo.edu)) the Alliance Registration Office.
- After Registration Office confirms progression and ensures all data is up-to-date with Data Manager, the patient will be allowed to re-register to the trial.

Follow the OPEN enrollment procedures as detailed in [Section 4.5](#).

#### 4.7 Registration to Correlative and Companion Studies

##### 4.7.1 Registration to Substudy described in [Section 14.1](#)

There is one substudy within Alliance A091401. This correlative science study **must be offered to all patients** enrolled on Alliance A091401 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091401 is:

- Correlative Science, Alliance A091401-ST1 ([Section 14.1](#))

If a patient answers “yes” to “I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above,” they have consented to participate in the substudy described in [Section 14.1](#). The patient should be registered to Alliance A091401-ST1 at the same time they are registered to the treatment trial (A091401). Samples should be submitted per [Section 6](#).

#### 4.8 Grouping Factors

- Enrollment Group:
  1. Initial Cohort (enrollment closed as of 02/02/2017)
  2. LPS
  3. UPS/MFH
  4. GIST

## 5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

### Pre-Study and Pre-Crossover (re-registration) Testing Intervals

- To be completed  $\leq 16$  DAYS before registration and re-registration: All laboratory studies, history and physical.
- To be completed  $\leq 28$  DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol
- To be completed  $\leq 42$  DAYS before registration and re-registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

	Prior to Registration AND Prior to Re-Registration *	Arm 1 (Nivolumab alone): Every 2 weeks	Arm 2 AND Crossover Patients Every 3 weeks x 12 weeks, then every 2 weeks	Post treatment follow up**	At PD, withdrawal, or removal***
<b>Tests &amp; Observations</b>					
History and physical, weight, PS****	X	X	X	X	X
Height	X				
Pulse, Blood Pressure	X	X	X		
Oxygen Saturation †	X	X	X	X	
Adverse Event Assessment $\pi$	X	X	X	X	
EKG, Echo or MUGA, CPK, troponin	X (F)				
Registration Fatigue/Uniscale Assessment	X(1)				
<b>Laboratory Studies</b>					
Complete Blood Count, Differential, Platelets	X	X (2)	X (2)	X	
Chemistry $\Psi$	X	X (2)	X (2)	X	
TSH	X	A(2)	A(2)		
Lipase		B(2)	B(2)		
Serologic Hepatitis B Surface Ag and Hepatitis C ab (physician discretion, not required)	X				
Serum or Urine HCG	X(3)				
Urinalysis		B(2)	B(2)		
<b>Staging</b>					
Central Pathology review for eligibility	X(4)				
CT or MRI of chest and of regions of tumor involvement	X(5)	C, D	C, D,E	C	X
<b>Correlative studies: For patients who consent to participate</b>					
Tissue samples (4)	<i>Baseline, and end of cycle 1. See <a href="#">Section 6.2</a></i>				
Blood samples (4)	<i>Weeks 1-16, PD/withdrawal/removal. See <a href="#">Section 6.2</a></i>				

- \* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained  $\leq 16$  days prior to treatment. Labs completed prior to re-registration may be used for day 1 of cycle 1 if obtained  $\leq 16$  days prior to treatment.
- \*\* Physical examination, adverse event assessment, labs (CBC and chem), and staging scans (if due per footnote C) are required 4 weeks (+/- 7 days) after the end of treatment.
- \*\*\* Patients who do not progress on treatment (i.e. removal for toxicity or withdrawal of consent) are followed every 6 months for both survival and disease status for at least three years post-randomization or until death, whichever comes first. Upon progressive disease (at any time), survival information is required every 6 months for 3 years. See also [Section 12](#).
- \*\*\*\* Drug dosages need not be changed unless the calculated dose changes by  $\geq 10\%$ .
- † Oxygen saturation should be assessed at rest and after 1 minute walk.
- $\pi$  Solicited AEs are to be collected starting at baseline until off treatment (See [Section 9.1](#)). Routine AEs are to be collected starting after registration. See [Section 9.3](#) for expedited reporting of SAEs.
- $\Psi$  Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
  - 1 To be completed after pre-registration and prior to registration ( $\leq 21$  days prior to treatment), see [Section 1.9](#) and [Appendix I](#). NOT required for re-registration.
  - 2 Labs may be performed +/- 3 days from date required.
  - 3 For women of childbearing potential (see [Section 3.2](#)). Must be done  $\leq 7$  days prior to registration. Also, must be done  $\leq 7$  days prior to re-registration.
  - 4 See [Section 6.2](#). Central pathology review is only required for registration, not required for re-registration.
  - 5 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Supporting documentation is to be submitted, per [Section 6.1.1](#).
- A Every 6 to 8 weeks.
- B Perform every 4 weeks x 4 in arm 1 (nivolumab alone). Perform every 3 weeks x 4, then every 2 weeks x 1 in arm 2 and crossover to dual agent therapy (nivolumab + ipilimumab).
- C Every 6 weeks for 12 weeks, then every 8 weeks until evidence of progression or relapse. Scans may be performed +/- 7 days from scheduled date. During the first 12 weeks of therapy, patients can be considered for continuation of treatment (see [Section 7.1](#) for further details and footnote D below). Confirmatory scans to be obtained at least 4 weeks following documentation of objective response (see [Section 11.0](#)). Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. For patients receiving initial treatment beyond 2 years from randomization date; scans may be performed every 3 months for year 3, every 4 months for year 4, every 6 months for year 5 and then yearly thereafter. One confirmatory scan continues to be required if patient achieves a response for the first time and during this period. Thereafter, returning to the assessment schedule.
- D If there is evidence of progression in the first 12 weeks, treatment is allowed to be continued. The patient's baseline assessment is now the 1<sup>st</sup> assessment showing progression (not the pre-study disease assessment) and is used for the remainder of the patient's initial treatment assignment (not crossover). Contact the Data Manager or Study Chair for questions. If this occurs, an additional scan is to be scheduled 4 weeks from the regular scan (i.e. at week 10 or 16). Thereafter, the patient will have a scan every 8 weeks. See also [section 7.1](#) for further information.
- E. **Crossover Patients Only:** For patients who crossover to dual agent therapy, a baseline scan is required  $< 28$  days prior to re-registration. After initiation of dual agent therapy scans are every 6 weeks for 12 weeks, then every 8 weeks until evidence of progression or relapse (scans may be done +/- 7 days from due date). During the first 12 weeks of therapy, patients can be considered for continuation of treatment (see [Section 7.1](#) for further details and footnote D above with the appropriate reset for baseline disease measurement. Contact the Data Manager or Study Chair for questions). Confirmatory scans are to be obtained at least 4 weeks following documentation of objective response (see [Section 11.0](#)). Response assessment should include assessment of all sites of disease and use the same imaging method as was used at the baseline measurements associated with crossover. For patients receiving crossover

treatment beyond 2 years from date of crossover, scans may be performed every 3 months for year 3, every 4 months for year 4, every 6 months for year 5 and then yearly thereafter. One confirmatory scan continues to be required if patient achieves a response for the first time and during this period. Thereafter, returning to the assessment schedule.

- F. For patients with evidence of CHF, MI, cardiomyopathy, or myositis a cardiac evaluation including lab tests and cardiology consultations as clinically indicated are required prior to study including EKG, CPK, troponin, ECHO or MUGA.

## 6.0 DATA AND SPECIMEN SUBMISSION

### 6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <<https://ctepcore.nci.nih.gov/iam>>) and the appropriate Rave role (Rave CRA, Read-Only, CRA [Lab Admin, SLA, or Site Investigator]) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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

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

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

#### 6.1.1 Supporting documentation

This study requires supporting documentation for screening, on study, response and progression. Supporting documentation will include “Central Pathology Review Form,” radiology report, pathology report, clinic note. These must be submitted at the following time points:

- Screening: Site will be required to upload the “Central Pathology Review Form” confirming eligibility onto the screening form.
- On study: clinic note, radiology report of baseline study scan only, and pathology report establishing diagnosis
- Response: radiology report
- Progression: radiology report and pathology report (if applicable); clinic note for patients deemed to have progressive disease by virtue of symptomatic deterioration (see [section 11.4.5](#))

## 6.2 Specimen collection and submission

### 6.2.1 Overview of specimen collection and submission

For patients registered to substudy A091401-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudy planned for Alliance A091401-ST1, although patient participation is optional. Serum studies, tumor and peripheral blood mononuclear cell (PBMC) genetic analysis and PBMC flow cytometry will be performed. Rationale and methods for the scientific components of these studies are described in [Section 14.0](#). For patients who consent to participate, tissue and blood will be collected at the following time points for these studies:

	Pre-treatment (not applicable to crossover to dual agent therapy)	Arm 1: Weeks 3,5,9, 11,13*	Arm 2: Weeks 4,7,10, 13,15*	Crossover to dual agent therapy Weeks 1,4,7,10,13 & 15	End of Cycle 1 (6 weeks): Includes crossover to dual agent therapy	End of Treatment	PD, withdrawal, or removal	Storage/ Shipping conditions	Submit to:
<b>Mandatory for <u>all</u> patients pre-registered to A091401:</b>									
Archival FFPE tumor block OR 1 representative H&E and 20 unstained tissue slides **	X(1)							See <a href="#">Section 6.2.3</a>	OSU
<b>For patients registered to A091401-ST1, submit the following:</b>									
Fresh tumor biopsy	X(2)			X (3)	X			See <a href="#">Section 6.2.4</a>	OSU
Peripheral whole blood (EDTA)***	1 x 10 mL							See <a href="#">Section 6.2.5</a>	OSU
Peripheral whole blood (non-additive red top) Ω	1 x 10 mL	1 x 10 mL	1 x 10 mL	1 x 10 mL		1 x 10 mL	1 x 10 mL	See <a href="#">Section 6.2.5</a>	OSU
Peripheral whole Blood (green top heparin) Ψ	2 x 10 mL	2 x 10 mL	2 x 10 mL	2 x 10 mL		2 x 10 mL	2 x 10 mL	See <a href="#">Section 6.2.5</a>	OSU

\* Correlative time points for blood-should be drawn on the visit and day of treatment for each arm. See [Section 5.0](#) for dates of clinical assessments. All correlative time points have a window of  $\pm 1$  week. Correlates obtained outside these windows may be included in analysis after discussion with the Study Chair.

\*\* Tumor block is preferred. If site does not have 20 slides, send as many as possible, up to 20. This is for mandatory pathology review, PD-L1 expression in tumor and tumor infiltrating lymphocytes (TIL) and TIL expression by IHC. For patients who opt into tissue bank (Model Consent Question#2 SAMPLES FOR FUTURE RESEARCH STUDIES). Left over tissues will be stored at the Alliance Biorepository at OSU for future unspecified research.

- \*\*\* Germline DNA to be used for analysis described in [Section 14.0](#). It is strongly encouraged that the whole blood sample for germline DNA is collected prior to the initiation of study treatment. However, this sample collection may take place during later clinical visit while the patient is on study.
- Ω Serum to be used for biomarker analyses described in [Section 14.0](#). Plasma isolated from heparin green top tubes processed for PMBC's can substitute for serum if necessary.
- Ψ PBMCs to be used for flow cytometry and/or genomic analysis described in [Section 14.0](#).
  - 1 Collect/submit within 3 days from pre-registration.
  - 2 Blocks/cores to be used for biomarker/TMA analyses described in [Section 14.1](#). If sufficient archival tissue (block, unstained slides) is available from a metastatic or unresectable lesion, baseline tumor biopsy may be foregone after discussion with the Study and/or Correlate Chair. Baseline biopsy can be performed anytime between registration and first day of study therapy. Archival block or unstained slides may suffice for baseline biopsy if at least 80% tumor (based on local histopathology review) and adequate sample is available for analysis. See [Section 6.2.4](#) for instructions.
  - 3 Collect tissue at baseline (prior to initiation of dual agent therapy, after progression on single agent nivolumab).

### 6.2.2 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: <http://bioms.allianceforclinicaltrialsinoncology.org> using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or [Bioms@alliancenctn.org](mailto:Bioms@alliancenctn.org). For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or [Bioms@alliancenctn.org](mailto:Bioms@alliancenctn.org).

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A091401), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

All specimens should be sent to the following address:

Alliance Biorepository at Ohio State University (OSU)  
Department of Pathology  
Polaris Innovation Centre  
2001 Polaris Parkway  
Columbus, OH 43240  
Tel: 614-293-7073 Fax: 614-293-7967

### **6.2.3 Collection and processing for histopathology review (Mandatory for all patients))**

Consistent and accurate histologic grading is important for this study. Archival FFPE tumor block (preferred) **OR** 1 representative H&E and 20 unstained tissue slides (thickness of 4-5 microns) from the diagnostic biopsy must be submitted. The submission should be taken from the highest grade area as identified by your local pathologist/investigator. This will be used for central pathology review and PD-L1 testing in tumor, tumor infiltration lymphocytes (TILs) and TIL expression.

Blocks which contain minimal amounts of tissue specimen based on local review or that are very thin should not be submitted unless the block is the only representative tissue for the case. A de-identified surgical pathology report should be sent with all specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

**In addition to the pathology report, the institution must complete and submit the “Central Pathology Review Form” with the tumor block or slides to the Alliance Biorepository at OSU. Failure to submit this form with the specimens will delay turnaround time for central pathology review.** The top portion of the form must be completed by typing and cannot be handwritten. For Alliance members, the form may be found on the A091401 study page on the Alliance website under the “Supplemental Materials” tab. For non-Alliance institutions, the form can be found under “Miscellaneous” documents section of the CTSU A091401 study page ([www.ctsu.org](http://www.ctsu.org)).

When shipping blocks and /or FFPE slides, it is important to avoid extreme heat. If environmental conditions indicate, specimens may be shipped in containers containing cold packs. The diagnostic slides must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. It is also important that blocks are shipped in appropriately padded and secure containers to avoid physical damage. Do not wrap blocks or slides in tissue or paper toweling that is in direct contact with the paraffin.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block.

The goal of the Alliance is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All slides/blocks may be returned with written request by the site.

### **6.2.4 Collection of fresh biopsy specimen (A091401-ST1)**

From patients who consent to A091401-ST1, fresh biopsy samples will be used for the analyses described in [Section 14.1](#) (Objective 2). Core biopsy samples will be taken at the following time points:

- Prior to start of treatment (anytime between registration and first day of study therapy). An archival block or unstained slides may suffice for fresh baseline biopsy

if at least 80% tumor (based on local histopathology review) and adequate sample is available for analysis.

- End of cycle 1 of therapy (week 6 of initial treatment assignment AND in addition week 6 of crossover dual agent therapy). This biopsy specimen is optional but encouraged.
- Prior to start of crossover to dual agent therapy after progression on single agent nivolumab. A fresh biopsy must be obtained for arm 1 patients who progress and are proceeding with crossover to dual agent therapy

The same metastatic tumor site should be biopsied at both time points, if feasible. Cores should be representative of tumor (preferably >80% tumor based on local histopathology review). A goal of 3-4 cores should be obtained, with 1-2 flash frozen in liquid nitrogen. But it is acceptable to send less if is not possible to obtain all of these:

- If 1 core is obtained, it should be placed in formalin and paraffin-embedded.
- If 2 cores are obtained, 1 should be placed in formalin and 1 should be flash frozen in liquid nitrogen
- If 3 cores are obtained, 2 cores should be flash frozen in liquid nitrogen and 1 should be placed in formalin
- If 4 cores are obtained, 2 cores should be flash frozen in liquid nitrogen and 2 should be placed in formalin

Label samples with the following identification:

- 1) Procurement date
- 2) Alliance patient number
- 3) Alliance study number (i.e. A091401-ST1)
- 4) Time point (baseline or week 6)
- 5) Tumor type (primary vs metastasis)

Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.

Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.

Remove the cryovial from liquid nitrogen and store the sample in a -80°C freezer (-65°C to -80°C acceptable) until ready for shipping on dry ice. **Flash frozen samples must be shipped overnight on dry ice.**

**If at least 80% tumor and adequate sample (based on local histopathology review) is available for analysis, then an archival block or unstained slides may suffice for fresh baseline biopsy (archival tissue is not applicable for baseline biopsy for patients crossing over to dual agent therapy, this requires fresh tissue).** Paraffin blocks of primary and, when available, metastatic tissue obtained from archival sarcoma tumor specimens should be sent to the Alliance Biorepository at Ohio State University. **Paraffin-embedded samples can be sent in ambient temperature.** Please specify the source of the tumor block (primary or metastatic site) and accompany it with a deidentified pathology report.

If, due to institutional policy, a block cannot be sent, 15 unstained slides (in addition to those sent for central pathology review) will suffice (thickness of 4-5 microns). Unstained slides

should be cut within 1 week of shipment. Charged slides are required. **After cutting, the slides should be refrigerated at 2-4°C and sent in ambient temperature.**

The goal of the Alliance Biorepository at OSU is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the OSU will be vacuum packed to prevent oxidation and will be stored at 4° C to minimize degradation of cellular antigens. For these reasons it is preferred that the Alliance Biorepository at OSU bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository at OSU if additional assurances with your hospital pathology department are required.

### 6.2.5 Blood sample submission (A091401-ST1)

For patients who consent to A091401-ST1, whole blood samples will be used for the analyses described in [Section 14.1](#). From consenting patients:

- Collect 10 mL of venous blood in lavender top (EDTA anticoagulant) vacutainer tube(s) at baseline. The tubes should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping. The sample should be placed in a biohazard bag shipped according to IATA guidelines the same day as the blood is drawn on a cold pack by overnight courier service to the Alliance Biorepository at OSU for germline DNA extraction.
- Collect 10 mL of peripheral venous blood in red top vacutainer tube(s) at the following time points:
  - Arm 1: Baseline, Weeks 3,5,9, 11, 13; End of treatment; PD, withdrawal or removal from study.
  - Arm 2: Baseline, Weeks 4, 7, 10, 13, 15; End of Treatment; PD, withdrawal, or removal from study.
  - Crossover to dual agent therapy upon progression on Arm 1: Weeks 1, 4, 7, 10, 13, 15; End of Treatment; PD, withdrawal, or removal from study.

Gently invert approximately 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot. Refrigerate the sample until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn on cold pack by overnight courier service to the Alliance Biorepository at OSU for serum preparation.

- Collect 2 x 10 mL of peripheral venous blood into green top (sodium heparin) vacutainer tubes at the following time points:
  - Arm 1: Baseline, Weeks 3, 5, 9, 11, 13; End of treatment; PD, withdrawal or removal from study.
  - Arm 2: Baseline, Weeks 4, 7, 10, 13, 15; End of Treatment; PD, withdrawal, or removal.
  - Crossover to dual agent therapy upon progression on Arm 1: Weeks 1, 4, 7, 10, 13, 15; End of Treatment; PD, withdrawal, or removal from study.

Invert tubes approximately 8-10 times to mix the sodium heparin solution. Specimens should be kept at room temperature until shipping. Samples should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn and shipped at ambient temperature by overnight courier service to the Alliance Biorepository at OSU for PBMC isolation. Please do NOT use cold pack during shipping for the whole blood sodium heparin (green top) samples.

Label samples with the following identification:

- 1) Procurement date
- 2) Alliance patient ID number
- 3) Alliance study number (i.e., A091401-ST1)
- 4) Time point (baseline, Week 1, etc)
- 5) Patient initials
- 6) Sample type

## 7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin  $\leq$  14 days of registration or of re-registration.

It is acceptable for individual therapy doses to be delivered  $\leq$  a 24-hour (business day) window before and after the protocol-defined date for a scheduled dose. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of immunotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Patients with locally advanced/unresectable and/or metastatic sarcoma of will be randomized in a 1:1 fashion to receive either nivolumab single agent or combination nivolumab + ipilimumab. Upon progression on a minimum of 10 weeks of nivolumab single agent, patients may crossover to dual agent therapy. See [Section 7.2](#) for further information.

Though treatment is every 2 or 3 weeks depending on the treatment arm, **a cycle will consist of 6 weeks in length** and therapy can be continued until patient develops progressive disease or unacceptable toxicity or withdraws from treatment. In the absence of these 3 events, treatment will continue for a maximum of 108 weeks (i.e. 18 cycles) on either arm. See [Section 7.1](#) for further information.

To determine response via RECIST v1.1, patients will undergo radiographic imaging every 6 weeks for 12 weeks, then every 8 weeks thereafter while on study treatment.

Duration of treatment in both arms: Up to 2 years.

### ARM 1

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
Nivolumab	3mg/kg IV over 30 minutes	Every 2 weeks	42 days

### ARM 2\*\*

Administer nivolumab prior to ipilimumab (follow institutional standard for timing between agents) as specified below:

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
nivolumab	3mg/kg IV over 30 minutes	Every 3 weeks	42 days
ipilimumab	1mg/kg IV over 90 minutes	Every 3 weeks	42 days

\*\*The above regimen will be followed for 4 doses, followed by:

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
nivolumab	3mg/kg IV over 30 minutes	Every 2 weeks	42 days

## 7.1 Treatment Decisions within the First Twelve Weeks of Therapy

Note: This section is applicable to initial treatment assignment, and to patients who are crossing over from the single agent nivolumab to combination treatment.

Patients who progress by imaging (See [Section 11.4.3.2](#)) during the first 12 weeks of therapy may continue treatment, at the discretion of the patient and treating investigator. These patients must meet all of the following in order to be eligible to continue therapy:

- No more than 4 new lesions. The sum of the longest diameter (SHORT diameter for LN) of target lesions and the new lesions are less than 40% increase from the baseline.
- Patients must be clinically stable with no change in performance status due to disease progression
- No indication for immediate alternative treatment
- Patient [assessed by the investigator] is showing clinical benefit and tolerates study drug. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.
- The time of progression is noted from the first assessment that exceeds standard criteria

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

If the decision is made to continue treatment after progressive disease is identified within the initial 12 weeks (and criteria above are met), then the patient may continue therapy for a maximum of 4 weeks. **Note:** At this time, the baseline scan to use for further assessments of disease status is reset to this assessment. After 4 weeks a scan is to be repeated. If the scan shows progression compared to the scan 4 weeks prior, they should be removed from protocol therapy. If the scan shows stable disease or response, compared to the scan 4 weeks prior, they can remain on protocol therapy should they choose to and the suspected initial progression date and assessment is considered the baseline scan to use for until further PD is evident. See section [11.4.3.2](#) for more information for determining objective status and [section 12.1](#) for information regarding duration of therapy. Scan schedule will resume routine schedule, as per [Section 5.0](#) footnote D.

Patients who have progression AFTER the initial 12-week period will be removed from protocol therapy in arm 2 (arm 1 patients may elect to cross over to dual agent therapy with progression after a minimum of 10 weeks of single agent nivolumab).

## 7.2 Crossover to Dual Agent Nivolumab and Ipilimumab upon Progression on Arm 1 (single agent nivolumab)

Upon documentation of progression on arm 1 and confirmation of eligibility criteria as per [Section 3.4](#), patients may be re-registered and initiate dual-agent therapy. All parameters outlined in [section 7.0](#) are applicable. NOTE: Treatment beyond progression in the first 12 weeks, as per [section 7.1](#), is applicable to patients receiving crossover dual agent therapy.

Administer nivolumab prior to ipilimumab (follow institutional standard for timing between agents) as specified below:

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
nivolumab	3mg/kg IV over 30 minutes	Every 3 weeks	42 days
ipilimumab	1mg/kg IV over 90 minutes	Every 3 weeks	42 days

\*\*The above regimen will be followed for 4 doses, followed by:

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
nivolumab	3mg/kg IV over 30 minutes	Every 2 weeks	42 days

Though treatment is every 2 or 3 weeks, **a cycle will consist of 6 weeks in length** and therapy can be continued until patient develops progressive disease or unacceptable toxicity or withdraws from treatment. In the absence of these 3 events, treatment will continue for a maximum of 108 weeks (i.e. 18 cycles) including the single agent nivolumab received prior to crossover to dual agent therapy.

To determine response via RECIST v1.1, patients will undergo radiographic imaging every 8 weeks while on study treatment.

## 8.0 DOSE AND TREATMENT MODIFICATIONS

### 8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care.

Please refer to the Nivolumab Investigator Brochure or [Appendix III](#) to the protocol for toxicity management algorithms which include recommended treatment guidelines for toxicity associated with nivolumab and ipilimumab. These algorithms provide recommended guidelines for treating physicians.

#### 8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

#### 8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

#### 8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure (steroid supplementation should be at physiologic dosing or as described in [section 8.1.10](#)); hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols.

#### 8.1.4 Antiemetics may be used at the discretion of the attending physician.

#### 8.1.5 Diarrhea: Please see Section [8.1.10](#) for further description of immune mediated colitis. All therapies for diarrhea are allowed on this protocol at the discretion of the treating investigator.

#### 8.1.6 Radiation therapy

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

#### 8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. *J Clin Oncol* 24(19): 3187-3205, 2006.

**Epoetin (EPO):** Use of epoetin in this protocol is permitted at the discretion of the treating physician.

#### **Filgrastim (G-CSF) and sargramostim (GM-CSF)**

1. Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
2. Filgrastim/pegfilgrastim and sargramostim may not be used:
  - a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
  - b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction

(sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.

- c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

**8.1.8 Surgery:** Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of sarcoma. Study drug should be held for a maximum of 42 days. If the patient requires an interruption of > 42 days, then they will be removed from protocol therapy.

**8.1.9 Infusion reactions:** See [Appendix V](#) for management.

**8.1.10 Immune related toxicity:** Both ipilimumab and nivolumab can lead to a variety of immune manifestations. The following supporting care guidelines are given for specific toxicities:

- **Colitis:** Typical symptoms of immune-mediated enterocolitis are diarrhea, abdominal pain, mucus or blood in stool, with or without fever. Consider evaluation to ensure that there is not an infectious etiology. Consider treatment with anti-diarrheals or corticosteroids at the discretion of the treating physician. Evaluation by GI should be considered. Treating physicians should consider the risk of perforation with colitis and utilize anti-diarrheals with this in mind. Recommend evaluation for all patients for additional causes including C. diff, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.
- **Pneumonitis:** Patients with suspected pneumonitis should undergo full evaluation, which may include CT scan, PFTs, O2 saturation, bronchoscopy. Treatment may involve steroids (any grade pneumonitis) and possibly empiric antibiotics, at the discretion of the treating physician. Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Consider that new lung nodules may represent sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine, as per the bullet below (“vaccinations”).
- **Nephritis:** For suspected nephritis, the patient should be evaluated by nephrology and considered for renal biopsy.
- **Hepatitis:** For hepatitis, close monitoring with serial LFTs should be instituted. Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including gall bladder inflammation/pancreatitis.
- **Endocrinopathy:** At the discretion of the treating physician: consider endocrine consult, draw all appropriate labs (such as cortisol, ACTH, TSH and T4), perform any appropriate imaging (such as pituitary MRI), and supplement any deficiency. It is recommended to perform any clinically indicated laboratory evaluation of pituitary function before beginning steroid therapy or replacement therapy of any kind.
- **Gastritis:** In patients with nausea or vomiting consider evaluation for upper GI inflammation and other immune related events.

- **Rash:** Consider dermatology consult and skin biopsy, at the discretion of the treating physician. Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically. Please be aware of the possibility that additional autoimmune events that may occur shortly after the appearance of skin rashes or pruritus and during the steroids withdrawal period.
- **Neuropathy:** Consider neurology consult for any grade 3 or 4 neuropathy, at the discretion of the treating physician.
- **Pancreatitis:** Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur with other immune mediated events including colitis, hepatitis, and gall bladder inflammation.
- **Immunosuppressive agents:** Steroids are recommended as first line intervention for the immune related toxicity of these drugs. Steroids should be started prior to obtaining results of any testing, based on clinical indications for steroid initiation. Specifically: Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 should be obtained to document baseline pituitary function which may be suppressed on treatment. Steroids should be tapered over 1 month if clinically appropriate, while monitoring for any return of toxicity. Potential second line agents are mycophenolate, cyclophosphamide, infliximab, IVIG, etc., at the discretion of the treating physician.
- **Vaccination:** Flu vaccine, pneumococcal vaccine, and any other relevant vaccines are recommended PRIOR to initiation of protocol therapy, at the discretion of the treating physician.

**8.1.11 Fatigue:** Fatigue is the most common adverse event associated with immune checkpoint therapy. Consider evaluation for associated or underlying organ involvement including pituitary disease, thyroid disease, and liver disease, or muscle inflammation

**8.1.12 Fever:** Patients may experience isolated fever during infusion reactions or up to several days after infusion. Continued fever over the course of 1-2 weeks may represent autoimmune events, or infection. Appropriate workup should be initiated, at the discretion of the treating physician.

**8.1.13 Supplementation:** Electrolyte abnormalities should be adequately corrected with appropriate supplementation upon discovery.

## 8.2 Dose Modifications

- If study drug/s is(are) held for >6 weeks, study drug/s will be discontinued.
- Any patients with autoimmune toxicity who require additional immune suppressive treatment beyond steroids should go off study drug/s.
- Patients may be dose-delayed for toxicity evaluation and restarted depending on results.
- Any patient started on corticosteroids initially for a presumed autoimmune adverse event, and subsequently found to not have an autoimmune etiology of their adverse event, may resume therapy after a 2 week observation period without recurrence of symptoms.
- Study drug/s should not be restarted until steroids have been tapered down to 5mg of prednisone equivalent.
- Patients requiring > two dose delays for the same event should go off study drug.
- Descriptors below utilize CTCAE version 4.03. AERs reporting may be required for some adverse events (See [Section 9.0](#))

### 8.2.1 Dose Levels

See [Section 7.0](#) and [Section 7.2](#) for the dosing schema for both arms. **No dose reductions will be made during this study, only dose delays.** Therefore there is only 1 dose level.

**The following tables provide protocol specific instructions for continuing administration of the investigational agent.**

*Generally we strongly encourage early evaluation, withholding drug, and appropriate treatment as indicated in the management tables and following event specific guidelines.*

### 8.2.2 Dose Modification

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab and Ipilimumab
Grade 1	Continue on protocol therapy*
Grade 2	Continue on protocol therapy.*
Grade 3	Hold** until ≤ Grade 1. Resume nivolumab/ipilimumab at same level*
Grade 4	Off protocol therapy
*Steroid use does not require discontinuation of protocol therapy.	
**Any grade Steven Johnson syndrome requires discontinuation of protocol therapy.	
Recommended management: See Skin AE management algorithm	

Liver Function ALT AST Bilirubin	Management/Next Dose for Nivolumab and Ipilimumab
Grade 1	Continue protocol therapy*
Grade 2	Hold therapy until ≤ grade 1 then restart nivolumab/ipilimumab at same dose.*
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
*Steroid use does require discontinuation of protocol therapy.	
Recommended management: see Hepatitis AE management algorithm	

<b>Colitis**</b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy*
Grade 2	Hold therapy until $\leq$ Grade 1*, then restart nivolumab at same dose. Discontinue ipilimumab.
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy.
See GI AE Algorithm for management of symptomatic colitis. *Steroid use does not require discontinuation of protocol therapy. **Follow this table for diarrhea when the workup shows objective evidence of autoimmune colitis.	
Recommended management: see GI AE management Algorithm	

<b>Diarrhea**</b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy
Grade 2	Hold until $\leq$ Grade 1*, then restart nivolumab/ipilimumab at same dose.
Grade 3	Hold until $\leq$ Grade 1*, then restart nivolumab/ipilimumab at same dose.
Grade 4	Hold until $\leq$ Grade 1*, then restart nivolumab/ipilimumab at same dose.
*Steroid use does not require discontinuation of protocol therapy. **Follow this table for diarrhea when the workup shows no objective evidence of autoimmune colitis	

<b>Pancreatitis**</b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 2	Continue on protocol therapy*
Grade 3	Hold therapy until $\leq$ grade 2 then restart nivolumab/ipilimumab at same dose.*
Grade 4	Off protocol therapy
*Steroid use does require discontinuation of protocol therapy. **Patients who have asymptomatic amylase or lipase elevation may have a self-limited course and may continue therapy.	

<b>Pneumonitis</b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Hold dose pending evaluation. Resume nivolumab/ipilimumab if lymphocytic pneumonitis is excluded.*
Grade 2	Hold until $\leq$ Grade 1*, then restart nivolumab/ipilimumab at same dose.
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
*Steroid use does require discontinuation of protocol therapy.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

<b><u>Gastritis, nausea, vomiting</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy*
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume nivolumab/ipilimumab at same dose level after resolution to Grade $\leq$ 1.*
Grade 3	Hold pending evaluation until $\leq$ Grade 1. Resume nivolumab at same dose level.* If symptoms do not resolve within 7 days with symptomatic treatment, patients should go off nivolumab. Discontinue ipilimumab.
Grade 4	Off protocol therapy
*Steroid use does not require discontinuation of protocol therapy.	

<b><u>Fatigue</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy.
Grade 2	Continue protocol therapy.
Grade 3	Hold until $\leq$ Grade 2. Resume nivolumab/ipilimumab at same dose level.*
*Steroid use does not require discontinuation of protocol therapy.	

<b><u>Neurologic events **</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Hold dose pending evaluation. Once evaluation is complete, resume nivolumab/ipilimumab at same dose level.*
Grade 2	Hold dose pending evaluation and observation. Hold until $\leq$ Grade 1 and then resume nivolumab/ipilimumab at same dose level.*
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
*Steroid use does require discontinuation of protocol therapy. **Patients with any grade CNS events of aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, polymyositis, rhabdomyolysis, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study once diagnosed.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

<b><u>Endocrine Toxicity**</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy.*
Grade 2	Hold until $\leq$ Grade 1 and patients are on a stable replacement hormone regimen, then resume nivolumab/ipilimumab at same dose level.*
Grade 3	Off protocol therapy.***
Grade 4	Off protocol therapy
*Steroid use for isolated thyroid disease or testosterone deficiency does not require discontinuation of protocol therapy. Steroid use for any other form of endocrine toxicity does require discontinuation of therapy. **Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events and removed from protocol therapy. Also, note patients with thyroiditis may be retreated with immunotherapy while on replacement therapy. ***Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored.	
Recommended management: See Endocrine Management Algorithm	

<b>Fever</b>	<b>Management/Next Dose for Nivolumab</b>
Grade 1	Continue protocol therapy. May hold if needed for evaluation, then resume nivolumab/ipilimumab at same dose level.*
Grade 2	Hold until $\leq$ Grade 1. Resume nivolumab/ipilimumab at same dose level.*
Grade 3	Hold until $\leq$ Grade 1. Resume nivolumab/ipilimumab at same dose level.*
Grade 4	Off treatment
*Steroid use does not require discontinuation of protocol therapy.	
See Appendix V regarding infusion reactions.	

<b><u>Renal toxicity:</u> Creatinine increased, hematuria</b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy.*
Grade 2	Hold until $\leq$ Grade 1. Resume nivolumab/ipilimumab at same dose level.*
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
*Steroid use does require discontinuation of protocol therapy.	
Recommended management: AE management guidelines	

<b><u>Infusion Reaction</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
Grade 1	Continue protocol therapy.*
Grade 2	Hold until $\leq$ Grade 1. Resume nivolumab/ipilimumab at same dose level.*
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
*Steroid use does not require discontinuation of protocol therapy.	
Recommended management: see <a href="#">Section 8.1.9</a> and <a href="#">Appendix V</a> management guidelines	

<b><u>Cardiac *</u></b>	<b>Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities</b>
<b><u><math>\leq</math> Grade 1</u></b>	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
<b><u>Grade &gt;2 with suspected myocarditis</u></b>	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
<b><u>Grade &gt;2 with confirmed myocarditis</u></b>	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
*Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin	
**Patients with evidence of myositis without myocarditis may be treated according as “other event”	
<u>Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.</u>	

<b><u>ALL OTHER EVENTS (Note 1)</u></b>	<b>Management/Next Dose for Nivolumab and Ipilimumab</b>
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1, then resume nivolumab/ipilimumab at same dose level.
Grade 3	Off protocol therapy (exceptions noted below in note 2)
Grade 4	Off protocol therapy
<p>Note: 1. Modifications are applicable to toxicity that is deemed related to study drug (attribution of possible, probable, or definite).</p> <p>Note 2. For any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment, nivolumab and ipilimumab should be discontinued.</p>	
Recommended management: As clinically indicated	

All other Grade  $\geq$  3 events including anemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, hypermagnesemia, hypoglycemia, hyperglycemia, elevated amylase or lipase that is deemed unrelated to drug (attribution of unrelated or unlikely) does not require change in dose.

Lymphopenia of any grade does not require change in dose.

### **8.2.3 Dose Modifications for Obese Patients**

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

## 9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

### 9.1 Routine adverse event reporting (solicited)

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in [Section 5.0](#). For this trial, "Adverse Events: Baseline", "Adverse Events: Solicited" and "Adverse Events: Other" are used for routine AE reporting in Rave.

**Solicited Adverse Events:** The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Hypothyroidism	Endocrine disorders
Abdominal Pain	Gastrointestinal disorders
Diarrhea	Gastrointestinal disorders
Nausea	Gastrointestinal disorders
Fatigue	General disorders and administration site conditions
Blood bilirubin increased	Investigations
Anorexia	Metabolism and nutrition disorders
Arthralgia	Musculoskeletal and connective tissue disorders
Cough	Respiratory, thoracic, and mediastinal disorders
Dyspnea	Respiratory, thoracic and mediastinal disorders

### 9.2 Routine adverse event reporting (not solicited)

In addition to the solicited adverse events listed in [Section 9.1](#), the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

**\*Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

- a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
- b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

### 9.3 Expedited Adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

**9.3.1 Late Phase 2 and Phase 3 Studies:** Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE  $\leq$  30 Days of the Last Administration of the Investigational Agent/Intervention <sup>1,2</sup>

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

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

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

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for  $\geq$  24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

<p>5) A congenital anomaly/birth defect.</p> <p>6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).</p>				
<p><b>ALL SERIOUS</b> adverse events that meet the above criteria <b>MUST</b> be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
<b>Hospitalization</b>	<b>• Grade 1 Timeframes</b>	<b>• Grade 2 Timeframes</b>	<b>• Grade 3 Timeframes</b>	<b>Grade 4 &amp; 5 Timeframes</b>
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	
<p><b>NOTE:</b> Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR</p> <p><b><u>Expedited AE reporting timelines are defined as:</u></b></p> <ul style="list-style-type: none"> <li>○ “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.</li> <li>○ “10 Calendar Days” - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.</li> </ul>				
<p><sup>1</sup> Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p><b>Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:</b></p> <ul style="list-style-type: none"> <li>• All Grade 4, and Grade 5 AEs</li> </ul> <p><b>Expedited 10 calendar day reports for:</b></p> <ul style="list-style-type: none"> <li>• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization</li> <li>• Grade 3 adverse events</li> </ul> <p><sup>2</sup> For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.</p>				

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:**

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Alliance A091401 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- Treatment expected adverse events include those listed in [Section 10.0](#) and in the package insert.
- CTEP-AERS reports should be submitted electronically.
- When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at <http://ctep.cancer.gov/>). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.
- Death due to progressive disease should be reported as Grade 5 “Disease Progression” under the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- Pregnancy loss is defined in CTCAE as “Death in utero.” Any Pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, “Death neonatal” under the General disorders and administration SOC.

## 9.4 CAEPRs

### 9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726, IND #126336)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, June 18, 2018<sup>1</sup>

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<b><i>Anemia (Gr 2)</i></b>
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade <sup>2</sup>	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency <sup>3</sup>		
	Hypophysitis <sup>3</sup>		
	Hyperthyroidism <sup>3</sup>		
	Hypothyroidism <sup>3</sup>		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia) <sup>3</sup>	
		Eye disorders - Other (Graves ophthalmopathy) <sup>3</sup>	
		Eye disorders - Other (optic neuritis retrobulbar) <sup>3</sup>	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<b><i>Abdominal pain (Gr 2)</i></b>
	Colitis <sup>3</sup>		
		Colonic perforation <sup>3</sup>	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Diarrhea		<i>Diarrhea (Gr 3)</i>
	Dry mouth		<i>Dry mouth (Gr 2)</i>
		Gastritis	
		Mucositis oral	
	Nausea		<i>Nausea (Gr 2)</i>
	Pancreatitis <sup>4</sup>		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 3)</i>
	Fever		<i>Fever (Gr 2)</i>
	Injection site reaction		<i>Injection site reaction (Gr 2)</i>
IMMUNE SYSTEM DISORDERS			
		Allergic reaction <sup>3</sup>	
		Autoimmune disorder <sup>3</sup>	
		Cytokine release syndrome <sup>5</sup>	
		Immune system disorders - Other (GVHD in the setting of allotransplant) <sup>3,6</sup>	
		Immune system disorders - Other (sarcoid granuloma) <sup>3</sup>	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction <sup>7</sup>		
INVESTIGATIONS			
	Alanine aminotransferase increased <sup>3</sup>		<i>Alanine aminotransferase increased<sup>3</sup> (Gr 3)</i>
	Aspartate aminotransferase increased <sup>3</sup>		<i>Aspartate aminotransferase increased<sup>3</sup> (Gr 3)</i>
	Blood bilirubin increased <sup>3</sup>		<i>Blood bilirubin increased<sup>3</sup> (Gr 2)</i>
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		<i>Lymphocyte count decreased (Gr 2)</i>
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	<i>Hyperglycemia (Gr 2)</i>
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis) <sup>3</sup>	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy <sup>3</sup>	
		Facial nerve disorder <sup>3</sup>	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Guillain-Barre syndrome <sup>3</sup>	
		Myasthenia gravis <sup>3</sup>	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis) <sup>3</sup>	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis) <sup>3</sup>	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome <sup>3</sup>	
RENAL AND URINARY DISORDERS			
		Acute kidney injury <sup>3</sup>	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion <sup>3</sup>		
	Pneumonitis <sup>3</sup>		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia) <sup>3</sup>	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme <sup>3</sup>	
	Pruritus <sup>3</sup>		<i>Pruritus<sup>3</sup> (Gr 2)</i>
	Rash maculo-papular <sup>3</sup>		<i>Rash maculo-papular<sup>3</sup> (Gr 2)</i>
		Skin and subcutaneous disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous disorders - Other (Sweet's Syndrome) <sup>3</sup>		
	Skin hypopigmentation <sup>3</sup>		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

<sup>2</sup>Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

<sup>3</sup>BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis,

autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

<sup>4</sup>Pancreatitis may result in increased serum amylase and/or more frequently lipase.

<sup>5</sup>Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

<sup>6</sup>Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

<sup>7</sup>Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

**Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Leukocytosis

**CARDIAC DISORDERS** - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

**EAR AND LABYRINTH DISORDERS** - Vestibular disorder

**EYE DISORDERS** - Eye disorders - Other (iritocyclitis); Optic nerve disorder; Periorbital edema

**GASTROINTESTINAL DISORDERS** - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema limbs; Malaise; Pain

**HEPATOBIILIARY DISORDERS** - Bile duct stenosis

**IMMUNE SYSTEM DISORDERS** - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

**INFECTIONS AND INFESTATIONS** - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

**INVESTIGATIONS** - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)

**NERVOUS SYSTEM DISORDERS** - Dizziness; Headache; Intracranial hemorrhage

**PSYCHIATRIC DISORDERS** - Insomnia

**RENAL AND URINARY DISORDERS** - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Bronchospasm; Cough; Dyspnea; Hypoxia

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

**VASCULAR DISORDERS** - Flushing; Hypertension; Hypotension; Vasculitis

**Note:** BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### 9.4.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442, IND #126336)

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

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, March 29, 2019<sup>1</sup>

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

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Abdominal pain		
	Colitis <sup>2</sup>		<i>Colitis<sup>2</sup> (Gr 3)</i>
		Colonic perforation <sup>3</sup>	
	Constipation		
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			<i>Nausea (Gr 3)</i>
	Pancreatitis <sup>2</sup>		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			<i>Fatigue (Gr 3)</i>
	Fever		<i>Fever (Gr 2)</i>
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBIILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis) <sup>2</sup>		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder <sup>2</sup>		
		Immune system disorders - Other (GVHD in the setting of allotransplant) <sup>4</sup>	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis) <sup>2</sup>	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis) <sup>2</sup>		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder <sup>2</sup>		
	Guillain-Barre syndrome <sup>2</sup>		
	Headache		
	Myasthenia gravis <sup>2</sup>		
		Nervous system disorders - Other (immune-mediated encephalitis) <sup>2</sup>	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		<i>Pruritus (Gr 3)</i>
Rash maculo-papular			<i>Rash maculo-papular (Gr 3)</i>

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

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

<sup>2</sup>Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

<sup>3</sup>Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

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

<sup>5</sup>In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

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

<sup>7</sup>Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)<sup>2</sup>; Febrile neutropenia

**CARDIAC DISORDERS** - Conduction disorder; Restrictive cardiomyopathy

**EYE DISORDERS** - Extraocular muscle paresis<sup>5</sup>; Eye disorders - Other (retinal pigment changes)

**GASTROINTESTINAL DISORDERS** - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage<sup>6</sup>; Proctitis

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Flu like symptoms; Non-cardiac chest pain

**HEPATOBIILIARY DISORDERS** - Hepatic failure<sup>2</sup>

**IMMUNE SYSTEM DISORDERS** - Allergic reaction

**INFECTIONS AND INFESTATIONS** - Infection<sup>7</sup>

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

**METABOLISM AND NUTRITION DISORDERS** - Tumor lysis syndrome

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity

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

**NERVOUS SYSTEM DISORDERS** - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure

**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Depression; Insomnia

**RENAL AND URINARY DISORDERS** - Proteinuria

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation

**VASCULAR DISORDERS** - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

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

## 10.0 DRUG INFORMATION

### 10.1 General Considerations

- The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.
- It is not necessary to change the doses of all study agents due to changes in weight unless the calculated dose changes by  $\geq 10\%$

### 10.2 Nivolumab (BMS-936558, MDX-1106, ONO-4538 NSC #748726, IND #126336, IND holder: CTEP)

#### *Procurement*

Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

#### *Drug Ordering*

NCI -supplied agents may be requested by eligible participating investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

**No starter supplies will be provided. Study agents must be ordered after the patient is enrolled on the assigned treatment arm. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.**

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

#### *Investigator Brochure Availability*

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a

CTEP IAM account and the maintenance of an “active” account status, and a “current” password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

#### **Useful Links and Contacts**

- CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration: [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov)
- PMB Online Agent Order Processing (OAOP) application: <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>
- CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
- CTEP Associate Registration and IAM account help: [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov)
- IB Coordinator: [IBCoordinator@mail.nih.gov](mailto:IBCoordinator@mail.nih.gov)
- PMB email: [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov)
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

#### *Formulation*

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

#### *Storage and Stability*

Vials of Nivolumab injection must be stored at 2° - 8°C (36° - 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) for determination of suitability.

Shelf-life surveillance of the intact vials is ongoing. The administration of undiluted and diluted solutions of nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2° to 8°C (36° to 46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period. Caution: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

#### *Preparation*

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4

mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

#### *Administration*

Administer via intravenous infusion over 30 +/- 10 minutes through an intravenous line containing a 0.2-micron to 1.2-micron pore size, low-protein-binding polyethersulfone membrane in-line filter. It is not to be administered as an IV push or bolus injection. Flush the intravenous line with 0.9% NaCl after each dose. Do not mix nivolumab with, or administer as an infusion with other medicinal products.

#### *Drug Interactions*

The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction..

#### *Pharmacokinetics*

##### **Single dose nivolumab pharmacokinetics**

**Distribution:** The mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses.

**Half-life elimination:** The mean terminal half-life of a single dose of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. The mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg

##### **Multiple dose nivolumab pharmacokinetics**

**Distribution:** Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and AUC(TAU) in the studied range of 0.1 mg/kg to 10 mg/kg. Nivolumab accumulation with Q2W dosing frequency was in the range of 2.9 to 3.3 based on AUC(TAU), 2.0 to 2.4 based on Cmax, and 3.1 to 4.8 based on Cmin.

**Half-life elimination:** The mean of terminal half-life was 25.6 days and the typical clearance was 8.8 mL/h.

#### *Adverse Events*

Refer to CAEPR in [Section 9.4.1](#).

#### *Nursing Guidelines*

- Nivolumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids. Additionally combination therapy (with ipilimumab) tends to have a higher rate of immune mediated side effects.
- Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per [section 8.0](#) and monitor for effectiveness.

- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.
- Patients who are started on steroid therapy for any side effects of nivolumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper

### **10.3 Ipilimumab (BMS-734016, MDX-010, NSC#s 732442 and 720801, IND #126336, IND holder: CTEP)**

#### *Procurement*

Ipilimumab is an investigational agent supplied by the National Cancer Institute (NCI). Bristol-Myers-Squibb (BMS) will supply ipilimumab to the DCTD/NCI and will be distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

Drug Ordering: NCI-supplied agents may be requested by eligible participating investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

No starter supplies will be provided. Study agents must be ordered after the patient is enrolled on the assigned treatment arm. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all

agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

#### *Investigator Brochure Availability*

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an “active” account status, and a “current” password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

#### Useful Links and Contacts

- CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration: [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov)
- PMB Online Agent Order Processing (OAOP) application: <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>
- CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
- CTEP Associate Registration and IAM account help: [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov)
- IB Coordinator: [IBCoordinator@mail.nih.gov](mailto:IBCoordinator@mail.nih.gov)
- PMB email: [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov)
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

#### *Formulation*

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, non-pyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab Injection, 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

Component	50 mg/vial	200 mg/vial
Ipilimumab	53.5 mg	213.0 mg
Sodium chloride	62.6 mg	249.0 mg
TRIS hydrochloride	33.7 mg	134.3 mg
Pentacetic acid	0.42 mg	1.67 mg
Mannitol	107 mg	426 mg
Polysorbate 80	1.18 mg	4.69 mg
Sodium hydroxide		QS to pH 7.0
Hydrochloric acid		QS to pH 7.0
Water for Injection	QS to 10.7 mL	QS to 42.6 mL

Nitrogen	Processing agent
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### *Storage and Stability*

Ipilimumab Injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted 5 mg/mL or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose in PVC, non-PVC/non-DEPH or glass containers for up to 24 hours at (2°C to 8°C).

### *Preparation*

Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of the infusion. Withdraw the required volume of ipilimumab and transfer into an intravenous bag. Ipilimumab injection (5 mg/mL) may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 2 mg/mL. Mix the diluted solution by gentle inversion. Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 69°F to 77°F).

### *Administration*

Do not mix ipilimumab with, or administer as an infusion with, other products. Administer the diluted solution over 90 +/- 10 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding in-line filter. Ipilimumab must not be administered as an IV push or bolus injection. Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

### *Drug Interactions*

No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab.

### *Pharmacokinetics*

**Distribution:** V<sub>ss</sub>: 7.21L

**Half-life elimination:** Terminal: 14.7 days

**Renal impairment:** The effect of renal impairment on the clearance of ipilimumab was evaluated in subjects with mild (GFR < 90 and ≥ 60 mL/min/1.73m<sup>2</sup>; n=349), moderate (GFR < 60 and ≥ 30 mL/min/1.73m<sup>2</sup>; n=82), or severe (GFR < 30 and > 15 mL/min/1.73m<sup>2</sup>; n=4) compared to subjects with normal renal function (GFR ≥ 90 mL/min/1.73m<sup>2</sup>; n=350) in population PK analyses. No clinically important differences in the clearance of ipilimumab were found between subjects with mild to moderate renal impairment and subjects with normal renal function. No specific dose adjustment is necessary in subjects with mild to moderate renal impairment.

**Hepatic impairment:** The effect of hepatic impairment on the clearance of ipilimumab was evaluated in 76 subjects with mild hepatic impairment (total bilirubin 1 to 1.5 x ULN or AST < ULN) compared to 708 subjects with normal hepatic function (total bilirubin and AST ≤ ULN). No clinically important differences in the clearance of ipilimumab were found between subjects with mild hepatic impairment and normal hepatic function. Ipilimumab has not been studied in patients with moderate (total bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

### *Adverse Events*

Refer to CAEPR in [Section 9.4.2](#).

### *Nursing Guidelines*

- Ipilimumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
- Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Mild rash may be able to be managed topically. Rarely TENS can be seen. Instruct patients with any rash (especially a blistering/peeling rash) and fever and/or lesions in the mouth to seek immediate medical attention.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Patients who are started on steroid therapy for any side effects of Ipilimumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

## 11.0 MEASUREMENT OF EFFECT

Response and progression as primary endpoints will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).[47] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

### 11.1 Schedule of Evaluations:

**Initial Treatment (Assigned at Registration/Randomization):** For the purposes of this study, patients should be evaluated every 6 weeks for 12 weeks, and then every 8 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response. See [Section 7.0](#) for further details. Additionally, see [Section 7.1](#) for instructions for how to treat, rescan, and use the proper disease assessment (e.g. baseline, reset baseline, or crossover baseline) for comparison in patients who demonstrate progressive disease within the first 12 weeks of study participation. For patients receiving initial treatment beyond 2 years from randomization date; scans may be performed every 3 months for year 3, every 4 months for year 4, every 6 months for year 5 and then yearly thereafter. One confirmatory scan continues to be required if patient achieves a response for the first time and during this period. Thereafter, returning to the assessment schedule.

**Crossover Treatment:** Patients having crossed over to dual agent therapy following progression of disease while receiving single agent nivolumab (per [section 3.4](#)) should be evaluated every 6 weeks for 12 weeks, and then every 8 weeks thereafter. As per [section 5.0](#), patients must have imaging performed within 28 days of re-registration to dual agent therapy. This scan will be the baseline scan for patients to determine response to dual agent therapy. For patients receiving crossover treatment beyond 2 years from date of crossover, scans may be performed every 3 months for year 3, every 4 months for year 4, every 6 months for year 5 and then yearly thereafter. One confirmatory scan continues to be required if patient achieves a response for the first time and during this period. One confirmatory scan continues to be required if patient achieves a response for the first time and during this period. Thereafter, returning to the assessment schedule.

See [Section 7.0](#) for further details. Additionally, see [Section 7.1](#) for instructions for how to treat, rescan, and use the proper disease assessment for comparison for patients who demonstrate progressive disease within the first 12 weeks of study participation.

In all cases, supporting documentation of response and progression should be submitted, per [Section 6.1.1](#).

### 11.2 Definitions of Measurable and Non-Measurable Disease

#### 11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as  $\geq 2.0$  cm with chest x-ray, or as  $\geq 1.0$  cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is  $\geq 1.0$  cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is  $\geq 1.5$  cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: they have been demonstrated to grow by at least 0.5 cm from measurement prior to radiation.

### 11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis  $\geq 1.0$  to  $< 1.5$  cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis  $< 1.0$  cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

## 11.3 Guidelines for Evaluation of Measurable Disease

### 11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

### 11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.  
As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **Chest X-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions,

documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - 1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - 2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
    - 3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

### 11.3.3 Measurement at Follow-up Evaluation:

**Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**

- A subsequent scan must be obtained at least 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR). This is applicable to both response during initial treatment assignment and to response to crossover to dual agent therapy.
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see [Section 11.4.4](#)).
- If a scan shows progressive disease during the first 12 weeks of therapy and patient and treating physician elect to remain on treatment, imaging should be repeated within 4 weeks. If that imaging confirms progression, then that patient has progressive disease and therapy should be discontinued. See [Section 7.1](#) for further details.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

## 11.4 Measurement of Treatment/Intervention Effect

### 11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in [Section 11.2.1](#)) up to a maximum of 5 lesions, representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

**Note:** If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease. **Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm. **Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

#### 11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease ([Section 11.2.2](#)) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with [11.4.3.3](#).

**Important: Refer to [section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**

#### 11.4.3 Response Criteria

- 11.4.3.1** All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in [Section 11.1](#). Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

#### 11.4.3.2 Evaluation of Target Lesions

**Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**

- **Complete Response (CR):** All of the following must be true:
  - a. Disappearance of all target lesions.
  - b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see [Section 11.4.1](#)).
- **Progression (PD):** At least one of the following must be true:
  - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to  $\geq$  1.0 cm short axis during follow-up.
  - b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD ([Section 11.4.1](#)). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  - c. See [Section 11.3.2](#) for details in regards to the requirements for PD via FDG-PET imaging.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

#### 11.4.3.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

**Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**

- **Complete Response (CR):** All of the following must be true:
  - a. Disappearance of all non-target lesions.
  - b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to  $\geq$  1.0 cm short axis during follow-up.
  - b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target

lesion and target lymph node status. It must be representative of overall disease status change.)

- c. See [Section 11.3.2](#) for details in regards to the requirements for PD via FDG-PET imaging.

#### 11.4.4 Overall Objective Status

**Important: Refer to [Section 11.1](#) for a full description of the correct baseline scan to use due to the retreatment after PD during treatment in the 1<sup>st</sup> 12 weeks, as well as baseline scan to be used for crossover treatment.**

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

\* See [Section 11.4.3.1](#)

**11.4.5 Symptomatic Deterioration:** Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

#### 11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

## 12.0 END OF TREATMENT/INTERVENTION

### 12.1 Duration of Treatment

**12.1.1 CR, PR, or SD:** Patients who are in CR, PR or SD will continue on therapy for a total of 108 weeks. After treatment is discontinued, patients will be followed per the study calendar in [section 5.0](#).

#### 12.1.2 Disease Progression:

Any patient with disease progression must be removed from protocol therapy, with the exception of management as per [Section 7.1](#). In the 1<sup>st</sup> 12 weeks of therapy, patients are allowed to continue therapy in the face of progression, as long as they meet all required bullets as per [Section 7.1](#). Note that this is applicable to both the initial treatment assignment and to treatment once patients have crossed over to dual agent therapy.

After disease progression, patients should be followed for survival per the study calendar ([Section 5.0](#)).

**12.1.3 Discontinuation of study agent:** If the patient discontinues study agent for reasons other than withdrawal of consent, he or she should be followed for survival per the study calendar ([Section 5.0](#)).

### 12.2 Crossover

Any patient that is originally randomized to the Nivolumab alone arm (Arm 1) will have the option to cross over to the nivolumab + ipilimumab combination therapy **ONLY IF** they were removed due to disease progression. Eligibility must be evaluated as per [Section 3.4](#) and patients must be re-registered to the crossover portion of the study per [Section 4.6](#).

Once patients re-register and cross-over to the nivolumab + ipilimumab dual therapy, all cross over patients must have a scan  $\leq$  28 days of starting their new treatment as per [Section 5.0](#).

Crossover patients previously removed from Arm 1 for progression who were being followed for survival will no longer be followed by the survival schedule nor survival case report form but will proceed to the crossover treatment schedule, crossover test schedule, and crossover case report forms. Cycles/data collection will resume from the last treatment cycle patient received. Contact the data manager for assistance with RAVE data entry.

### 12.3 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) are replaceable for efficacy endpoints. They must still complete follow-up requirements as specified below:

Baseline, on-study and off-treatment notice data submission required.

#### **12.4 Extraordinary Medical Circumstances**

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

## 13.0 STATISTICAL CONSIDERATIONS

### 13.1 Study Overview

Our study is designed to evaluate both single agent nivolumab as well as dual agent nivolumab+ipilimumab. Confirmed response rate over the first 6 months of treatment is our primary endpoint. Patients experiencing response within 4 weeks of reaching 6 months beyond their randomization date, will be included if their repeat 4 week scan confirms response. Patients will be randomized to receive either monotherapy or dual therapy, not for direct comparisons across treatments, but to conduct two independent single arm phase II studies simultaneously. The sample size of the design has been selected to 1) maximize the possibility of performing subset analysis (within specific histologically defined cohorts), and 2) improve precision of secondary and correlative endpoints. Stratification factors will not be used for randomization as there will be no direct comparison between the arms. All treatment decisions and the evaluation of the primary endpoint will be based on RECIST v1.1.

In early October 2015, the study was suspended to pre-registration after an unprecedented rate of pre-registrations and greater than anticipated interest in the trial. The study design was modified to best serve this population, of which effective treatments are lacking, and in consideration of the known safety profile of the agents. The use of a single stage design was supported by CTEP/NCI, the Alliance Experimental Therapeutics Committee Co-Chair (G. Schwartz), and the A091401 study team.

With Update #04, the study was approved to include a crossover to the dual agent therapy for patients having experienced PD during treatment with single agent Nivolumab. Of note:

- Patients are allowed to crossover to the dual agent therapy and within a specific time period, despite progression occurring months before the implementation of the Protocol Update.
- Analyses will be exploratory in this patient group and careful consideration will be given to the data, as described within the Statistical Considerations.

**With Update #06**, the study was amended to evaluate treatment arms within patient groups defined as having tumors of one of the following histologic subtypes:

- LPS
- UPS/MFH
- GIST

In essence, this study is now a total of 8 independent phase II trials. Patient enrollment and accrual will not include those patients already enrolled to the initial cohort. Randomization will continue to be used, similar to the application within the initial cohort of patients. Here, patients having tumors of a one histologic subtype will be randomly assigned to one of the two treatment arms, only to reduce physician/patient selection bias. Randomizing membership will be the only stratification factor. The evaluation of all study endpoints will be repeated within these histologically defined subgroups and in the same manner as the initial study cohort was designed. However, the study designs will differ, by cohort, and as described within [section 13.1](#).

### 13.2 Primary Endpoint

To evaluate the confirmed response rate of single agent nivolumab, as well as dual agent nivolumab + ipilimumab, within patients having locally advanced/unresectable or metastatic soft tissue sarcoma.

With Update #06 - the study objectives will be evaluated within the initial cohort of patients enrolled, as well as within 3 cohorts of patients defined by the following histologic subtypes: LPS, UPS/MFH, and GIST.

### 13.3 Study Design

Primary Endpoint: Confirmed response over the first 6 months of treatment is our primary endpoint. Patients experiencing response within 4 weeks of reaching 6 months beyond randomization date, will be included if their repeat 4 week scan confirms response. (For example, a patient achieves response 10 days prior to having been enrolled for 6 months. The confirmation scan is to occur within 28 days (+/- 7 days), which is beyond 6 months. If confirmed as CR or PR, the patient will be classified in the analysis as having a confirmed response). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be considered evaluable for the primary endpoint. Patients will be included in the analyses according to the treatment they were randomized to. In addition, patients having experienced PD within the initial 12 weeks of treatment which fails to satisfy the criteria for PD at the subsequent confirmatory repeat scan will be considered as evaluable and subsequent cycles will be included in determining a patient's tumor response status for the primary endpoint. However, neither treatment nor disease assessment data beyond the date of crossover will be included in the evaluation of the primary endpoint and for those patients crossing to dual agent treatment from single agent treatment. Patients will additionally be censored at their most recent disease assessment prior to receiving any anti-cancer therapy after ending study treatment. The confirmed response rate will be estimated as the number of patients having a best objective tumor status of CR or PR lasting at least 4 weeks during the first 6 months of treatment, divided by the number of evaluable patients.

#### 13.3.1: Initial Study Cohort (Prior to Update #06):

Two independent phase II studies will be conducted concurrently and patients will be randomized to receive one of the two treatments.

Hypotheses: We will evaluate the confirmed response of both single agent nivolumab and dual agent nivolumab + ipilimumab. We are testing the hypothesis of a confirmed response rate being at most 5% (clinically inactive) versus a confirmed response rate of at least 20% (clinically active).

Design Characteristics (each treatment arm): Enroll a total of 38 evaluable patients to each arm. An arm demonstrating at least 5 confirmed responses will be considered as having sufficient evidence of promising activity in this population and may be proposed for larger studies in this population.

This design yields 90% power to detect a true confirmed response rate of at least 20%, with a 0.05 significance level (1-sided test) if the true confirmed response rate is 5%.

#### 13.3.2: LPS and UPS/MFH Cohorts (Added in Update #06):

Four (4) independent phase II studies will be conducted concurrently and patients will be randomized to receive one of the two treatments. Patients will be included in the analyses according to the treatment they were randomized to. We are looking for an early signal of efficacy, based on scientific data described in [Section 1.9](#) and available in June 2016 and indicating activity in these new cohorts.

Hypotheses: We will evaluate the confirmed response of both single agent nivolumab and dual agent nivolumab + ipilimumab. We are testing the hypothesis of a confirmed response rate being at most 5% (clinically inactive) versus a confirmed response rate of at least 25% (clinically active).

Study Design (for both treatment arms): Patient enrollment and accrual will not include those patients already enrolled to the initial cohort. We will enroll a total of 12 evaluable patients to each arm. An arm demonstrating at least 2 confirmed responses during the first 6 months of treatment will be considered as having sufficient evidence of promising activity in this population and may be proposed for larger studies in this population.

Design Characteristics (each treatment arm): This design yields 85% power to detect a true confirmed response rate of at least 25%, with a 0.15 significance level (1-sided test) if the true confirmed response rate is 5%.

### 13.3.3: GIST Cohorts (Added in Update #06):

Two (2) independent phase II studies will be conducted concurrently and patients will be randomized to receive one of the two treatments. Patients will be included in the analyses according to the treatment they were randomized to.

Hypotheses: We will evaluate the confirmed response of both single agent nivolumab and dual agent nivolumab + ipilimumab. We are testing the hypothesis of a confirmed response rate being at most 5% (clinically inactive) versus a confirmed response rate of at least 20% (clinically active).

Study Design (for both treatment arms): Patient enrollment and accrual will not include those patients already enrolled to the initial cohort. We will enroll a total of 24 evaluable patients to each arm. At the time we have 9 evaluable patients, we will perform a planned interim analysis. Any demonstration of confirmed response in these 9 patients during the first 6 months of treatment allows accrual to continue. An arm demonstrating at least 3 confirmed responses during the first 6 months of treatment in 24 evaluable patients will be considered as having sufficient evidence of promising activity in this population and may be proposed for larger studies in this population.

The study will not be suspended at the time of the planned interim analysis due unless there is an unexpectedly high enrollment rate or excessive toxicity. Excessive toxicity would be 3 or more patients a month in this population.

Design Characteristics (each treatment arm): This design yields 80% power to detect a true confirmed response rate of at least 20%, with a 0.10 significance level (1-sided test) if the true confirmed response rate is 5%. There is a 64% chance of stopping early, if the true confirmed response rate is at most 5%.

## 13.4 Secondary Endpoints

- Evaluating adverse event rates (NCI CTCAE v4.0), within each study treatment arm. Categorical data analysis will be used to summarize adverse event rates and as a maximum severity during treatment for each patient and AE classification.
- Evaluating duration of response, clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS), within each study treatment arm. Patients having PD within the first 12 weeks of starting treatment which is not a PD at their 4 week confirmation assessment will not be classified as having PD for time to event analyses. That is, estimates for response, CBR, and PD endpoints will not be censored at the first PD in such cases. Patients who are unable to continue treatment for a 4-week confirmation of PD occurring within the first 12 weeks of treatment will be counted as having PD at their first date of PD during the treatment period (eg, initial, crossover). In addition, disease assessment data beyond the date of crossover will not be included in the evaluation of the primary endpoint and for those patients crossing to dual agent treatment from single agent treatment. Such patients will be censored for estimating

duration of response, CBR, and PFS. Patients will be additionally censored at their most recent disease assessment prior to receiving any anti-cancer therapy after ending study treatment.

Kaplan-Meier methodology will be used to evaluate time to event endpoints: duration of response (time from first response to disease progression), PFS (time from randomization to the earliest of either disease progression or death from any cause), and OS (time from randomization to death from any cause). The CBR will be evaluated by counting up the number of patients with a response or stable disease (PR, CR, SD) and dividing by the total number of evaluable patients. Cumulative Incidence Function methodology may be used, as appropriate.

### 13.5 Exploratory and Correlative Endpoints

- The study is not powered to detect specific hypotheses, rather this data and analysis will help better identify patients that have the potential to benefit from this therapy and aid in designing larger Phase III studies. No direct comparisons will be made between the single and dual agent regimens. We will address the issue of multiple comparisons at the time of the analyses, which will be dependent on the number of hypotheses investigated.
- To assess the potential association between PD-L1 expression (by IHC) and clinical outcome, within each study treatment arm. Categorical data analysis and logistic regression will be used to evaluate the associations between PD-L1 expression (by IHC) and clinical outcome (eg, response, clinical benefit, progression-free survival, and survival). Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.
- To evaluate the associations between selected biomarker measured in serial peripheral blood and with clinical efficacy, within each study component. Summary statistics will be used to for describing changes across time. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots or individual patient plots. Categorical data analysis and logistic regression will be used to evaluate the associations between PD-L1 expression (by IHC) and clinical outcome (eg, response, clinical benefit, time to progression, progression-free survival, and survival). If there is suggestion of meaningful trend, methods such as linear mixed models may be used to characterize the pattern of change over time. Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.
- To evaluate the association between selected biomarker measured in tumor tissue with clinical efficacy, within each study component. Categorical data analysis and logistic regression will be used to correlated biomarkers with and clinical outcome (eg, response, clinical benefit, time to progression, progression free survival, and survival) within each study component. Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.
- Confirmed response and secondary endpoints will be evaluated in patients who crossover from single agent nivolumab to dual agent treatment following progression. The date used for the calculations of duration of response, TTP, PFS, and OS will be the date the patient initiated crossover treatment with dual agent therapy.

### 13.6 Total Sample Size, Accrual Duration, and Anticipated time to study completion

Although, we observed an unprecedented accrual rate for the initial portion of this study and pre-registered over 80 cases within 9-10 weeks (August-October 2015) and 15-17 cases within

5 hours (March 2016) and there is continued interest in this trial, we conservatively estimate that we can enroll a maximum of 2 patients per month within each of the histologic cohorts.

- If both GIST arms terminate at the interim analysis, we will need a maximum of 76 patients across 6 arms and will enroll these cases in 13 months.
- If at both GIST arms complete full enrollment, we will need a maximum of 110 patients. These cases will be enrolled in 24 months, without a suspension.

Therefore, we plan to enroll a minimum of 76 patients to a maximum of 110 patients across all 6 cohorts and arms (per Update #06), which includes 10% over accrual for non-evaluable patients. We will pre-register a maximum of 82 and 120 cases to obtain these enrollment figures and based on current screen failure rates at the time of central pathology review. The number of pre-registrations and registrations/randomizations to each group are summarized below:

**New Pre-registration & Enrollment, by Group (Per Update #06)  
(Two (2) Arms in 1 Group)**

Group	Step 1 <sup>a</sup>	Step 2 <sup>a</sup>	Group Total
LPS	28 (30) <sup>b</sup>	N/A	28 (30)
UPS/MFH	28 (30)	N/A	28 (30)
GIST	20 (22)	34 (38)	54 (60)
Step Total	76 (82)	34 (38)	110 (120)

a) Total for both arms.

b) Registered (Pre-registered)

Assuming that patients were allowed to remain in treatment for a maximum of 2 years and that we would need 6 months for quality assurance for the interim and final analyses, we estimate the maximum duration of the study to be an additional 36 months (3 years) from activation of Update #06.

Inclusive of those patients pre-registered and enrolled prior to Update #06 and for administrative purposes, this trial is targeting a maximum of 216 (i.e., 96 + 120) patients to be pre-registered and a maximum of 195 (i.e., 85 + 110) patients to complete final registration/randomization onto the study.

### 13.7 AE Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as

"possible", "probable", or "definite") that satisfy any of the following criteria for each arm separately and applies to the treatment patients were initially randomized to:

- If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e. when accrual is greater than 10 patients) have experienced a  $\geq$  grade 3 adverse event.
- If at any time, 2 patients have experienced a grade 5 adverse event (non -progressive disease).
- In addition, each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. We may suspend accrual after just 1 grade 5 AE, if needed.
- In addition, for patients who are assigned to single agent nivolumab and cross over to dual agent therapy, the same 3 conditions would trigger a temporarily suspension and would not allow further patients to re-register and receive dual agent therapy.

### 13.8 Accrual Monitoring Stopping Rule

At study activation, the expected accrual rate was 7 patients per month, and would take around 12 months to fully accrue. This study far surpassed the accrual stopping rule, as of mid-October 2015 after pre-registering 81 patients in 9-10 weeks and 15-17 patients in 5 hours in March 2016. Conservatively, we anticipate enrolling 6 patients per month (2 per cohort).

### 13.9 Primary Endpoint Completion Time Estimation (For clinicaltrials.gov reporting)

The primary endpoint is confirmed response, as discussed in detail in [section 13.2](#) and [13.3](#). The final analyses for the primary endpoint within all study cohorts are expected to be completed approximately 6.5 years after the study begins ([section 13.6](#)) and adjusted for activation of enrollment to the expansion cohorts associated with Update #6, so we expect that the primary endpoint completion time to be around 6.5years after initial study activation.

### 13.10 Descriptive Factors

- Histologic Subtype
  - Leiomyosarcoma
  - Liposarcoma
  - Malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma
  - Bone sarcomas
  - Vascular sarcomas
  - Ewing/Primitive neuroectodermal tumors
  - Synovial sarcoma
  - GIST
  - Other (specify)
- Disease Status: locally advanced vs metastatic vs both.

### 13.11 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and about 50% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table, based on enrollment prior to protocol Update #6 and for maximum enrollment to the trial:

<b>DOMESTIC PLANNED ENROLLMENT REPORT</b>					
<b>Racial Categories</b>	<b>Ethnic Categories</b>				<b>Total</b>
	<b>Not Hispanic or Latino</b>		<b>Hispanic or Latino</b>		
	<b>Female</b>	<b>Male</b>	<b>Female</b>	<b>Male</b>	
American Indian/ Alaska Native	4	4	0	0	8
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	6	5	2	2	15
White	74	81	8	6	169
More Than One Race	0	0	0	0	0
<b>Total</b>	87	90	10	8	195

**Ethnic Categories:** **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

**Not Hispanic or Latino**

**Racial Categories:** **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

**Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

**Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

#### 14.0 CORRELATIVE AND COMPANION STUDIES

**As of Update #06**, PD-L1 testing on FFPE tissue and on tumor infiltration lymphocytes (TILs); and characterization of TILs will be mandatory for all patient to participate. These mandatory assays will be done on FFPE tumor tissue required for all patients to submit (see [section 6.2.4](#)). If patients opted into “Fresh tumor biopsy”, these tests will also be performed on the fresh biopsy samples (see [section 6.2.4](#)). The rest of tests described below in section 14 are only applicable for patients who consent and registered to A091401-ST1.

For patients who enrolled to A091401 prior to protocol Update #06, FFPE tissue collected from patients who consented to future research question (question #2 SAMPLES FOR FUTURE RESEARCH STUDIES) will be used for testing PD-L1 expression on FFPE tissue and on tumor infiltration lymphocytes (TILs); and characterization of TILs.

There will be one substudy within Alliance A091401. This correlative science study **must be offered to all patients** enrolled on Alliance A091401 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091401 is:

## 14.1 Mandatory studies and optional Correlative Science (Alliance A091401-ST1)

### 14.1.1 Background

#### PDL-1 Expression in Sarcoma Cell Lines

In vitro models using sarcoma cell lines have documented very high PDL1 expression at baseline by Western blot (Figure 1) and by flow cytometry (Figure 1) that is also induced by interferon. Expression is noted in nearly 65% of the cell lines including synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumors, desmoplastic small round cell, osteosarcoma and chondrosarcoma.

#### PDL-1 Expression in Sarcoma Tumor Specimens

PDL-1 expression was evaluated in 50 sarcoma tumor specimens of various subtypes using immunohistochemistry with the use of a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8) and an automated assay developed by Dako. Greater than 1% PDL-1 expression was identified in 6/50 (12%) of samples (Table 1) There was evidence of macrophage and lymphocyte infiltration in the tumor, outside of the tumor, and both.

Median age 46 years (range, 22 - 76), 66% male. Disease status: 70% primary disease/locally recurrent, 26% metastatic and 4% unknown. Tumor, lymphocyte and macrophage PD-L1 expression was noted in 12%, 30% and 58%, respectively. Lymphocyte and macrophage infiltration was present in 98% and 90%, respectively. (Table 1)

Histology	n	% Tumor PD-L1 +	% Lymphocyte PD-L1 +	% Macrophage PD-L1 +
Angiosarcoma	3	0	100	100
GIST	14	27	100	100
Leiomyosarcoma	4	0	0	25
Liposarcoma	5	0	20	60
Synovial Sarcoma	3	0	33	0
Radiation associated pleomorphic sarcoma	1	100	100	100
Other	20	5	10	70
Overall	50	12	30	58

#### PD-L1 expression is not an established biomarker predictive of response

The significance of PD-L1 expression as a biomarker of response to checkpoint blockade with PD-1 inhibitors remains a controversial topic. PD-L1 expression remains a dynamic marker, that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute to varied PD-L1 expression.(30) Based on the initial phase I clinical data of the combination of ipilimumab and nivolumab in melanoma patients, patients with PD-L1 expression may be more likely to respond, however, lack of expression did not exclude responses. (29) These data suggest that either PD-L1 expression may change as a result of therapy with checkpoint blockade such as ipilimumab or nivolumab.

#### Tumor production of neoantigens may underlie response to immune checkpoint inhibition

Recently, a report by van Rooij et al associated a response to ipilimumab in a patient with melanoma with T cell recognition of a tumor-specific mutant protein, termed a 'neoantigen.' (31) To do this, they performed whole exome sequencing of the melanoma tumor tissue and tumor infiltrating lymphocytes (TILs) and identified >1000 tumor-specific mutations. They then utilized NetMHC, an online predictor of Class I major histocompatibility complex

(MHC)-specific affinities for specific sequences of 9-11 amino acids (32), to narrow the mutant sequences to 448 peptides predicted to bind with medium to high affinity to the patient's CD8+ T cells. These peptides were screened for binding with patient TILs, and they identified 3.3% of all patient CD8+ T cells reacted with a specific mutated epitope in the ataxia-telangiectasia and Rad3-related protein (ATR) pathway, suggesting this resulted in the clinical benefit seen in this patient.

Further support for neoantigen-specific immune surveillance has come from in vivo models of sarcoma. In a murine model of chemically-induced sarcomas arising in immune-deficient Rag2<sup>-/-</sup> mice, Matsushita et al reported that implantation into an immunocompetent murine host resulted in “immune editing” of the tumor, and tumors with a greater neoantigen load were frequently rejected by the new host. (33) Similar results were seen in a conditional Kras-p53 knockout mouse model. (34) Whereas the work of van Rooij et al and Matsushita et al suggests that certain key mutations predict response, DuPage et al and other authors (35) imply that a higher overall mutational load and resulting neoantigen burden may lead to efficacy. By associating mutational burden and additional analyses with clinical response, our data has the potential to determine which effect plays a greater role in the context of sarcoma.

The Chan lab at MSKCC has presented data at ASCO 2014 supporting the association between this patient-specific neoantigen analysis in melanoma with individual clinical benefit from ipilimumab [48]. Using whole exome sequencing of tumors and peripheral blood mononuclear cells, a neoantigen signature incorporating both mutational load and patient-specific neoantigens separated patients with prolonged clinical benefit from patients with progressive disease. Putative neoantigens were validated in vitro using patients' peripheral blood mononuclear cells and tumor infiltrating lymphocytes. These data are pending publication.

### **Peripheral Blood Lymphocyte Subsets Are Altered by Immune Therapy**

Recent investigations in patients with melanoma, lung cancer, and/or bladder cancer treated with nivolumab with or without ipilimumab have identified dynamic changes in the proportion of circulating CD8+ or CD4+ T effector (FoxP3-) or CD4+ T regulatory (FoxP3+) cells that express the proliferation marker Ki67 with therapy. The highest magnitude of change is seen about 1 week after the first doses of ipilimumab and nivolumab.

## **14.1.2 Objectives**

### **14.1.2.1 Objective 1: Neoantigen Analysis To identify overall mutational burden and number of putative tumor ‘neoantigens’ in sarcoma specimens**

- To explore the association between mutational and predicted ‘neoantigen’ burden in sarcoma samples with degree of clinical benefit in patients treated with nivolumab with or without ipilimumab

### **14.1.2.2 Objective 2: Characterization of Tumor Markers, Gene Expression, Infiltrating Lymphocytes and Circulating Lymphocytes**

- To investigate immune infiltrates in sarcoma tumors at baseline and following one cycle of therapy with nivolumab with or without ipilimumab
- To investigate subsets of circulating lymphocytes at baseline and at various timepoints during therapy with nivolumab with or without ipilimumab
- To analyze changes in gene expression in tumor samples at baseline and following one cycle of therapy with nivolumab with or without ipilimumab

- To explore associations between changes in tumor immune infiltrates, tumor gene expression, and circulating lymphocytes with degree of clinical benefit
- To evaluate PD-L1 expression in tumor and TILs and correlate with degree of clinical benefit

#### 14.1.2.3 Objective 3: Serum/Plasma Cytokines

To explore the composition of circulating factors, such as chemokines, cytokines, and other immune mediators in the blood at baseline and how they change with therapy with nivolumab with or without ipilimumab.

### 14.1.3 Methods

#### 14.1.3.1 Objective 1: Neoantigen Analysis

Tumor (and matched normal) whole exome and transcriptome sequencing for evaluation of mutational burden (MSKCC Genomics Core):

Tumor DNA, matched normal DNA, and tumor RNA will be extracted for whole exome and transcriptome analysis. Once DNA has been obtained and extracted, we will perform massively parallel sequencing of the whole exome of the tumor tissue and the available normal tissue. Genomic DNA will be captured via solution-based hybrid selection and sequenced on the Illumina HiSeq platform by the Genomics Core at MSKCC. Matched normal DNA will also be collected from whole blood and sequenced in conjunction with somatic tumor DNA. This is necessary to make variant calls in next-generation sequencing assays. It is not the intent of this analysis to utilize these samples to identify germline susceptibility mutations. However, in the course of investigating somatic sequence variations, germline susceptibility variants may be suggested by comparative germline sequencing. In addition, some somatic mutations are themselves directly suggestive of a germline predisposition (e.g. BRCA1).

Germline BAM files will not be separately analyzed in the future without additional informed consent, anonymization, and/or human subjects review.

The somatic sequencing data will be analyzed for base mutations, insertions, fusions, deletions, copy number alterations and in all target genes. Exon capture will be performed using the SureSelect Human All Exon 50MB kit (Agilent). Enriched exome libraries will be sequenced on the HiSeq 2000 platform (Illumina) to >100X coverage. Raw sequencing data will be mapped to the human reference genome. All filtered candidates will be annotated and manually reviewed (36) using the Integrated Genomic Viewer (IGV) (37). Mutations will be annotated using SnpEffect (38). In order to improve quality of calls in these FFPE samples, mutations will be analyzed using four callers: Somatic Sniper (39), VarScan (40), Strelka (41) and MuTect (42) then filtered by allelic frequency of each alteration in tumor (>10%) and normal (<3%), depth of coverage ( $\geq 7X$ ) and call quality. All calls made by only one caller will be manually reviewed using IGV (37).

Whole transcriptome tumor mRNA will be sequenced using next-generation sequencing. Briefly, after quantification and quality control, poly(A)RNA will be isolated and then fragmented and purified. The Fragmented Samples quality and yield are evaluated and will undergo Whole transcriptome Library preparation. Samples will be prepared using the ion one touch system II and Ion PI<sup>TM</sup>Template

OT2 200kit v2 Kit (Life Technologies). Enriched particles will be sequenced on a Proton sequencing system .

Bioinformatic Analysis - identification of candidate neoantigens (Chan, Wolchok, and Callahan Labs, MSKCC):

Bioinformatic techniques are being developed to use whole exome sequencing to identify candidate neoantigens. Neoantigens are modeled in silico by examining the components of antigen presentation on MHC (antigenicity) (43) and recognition by T-cells (immunogenicity). First, expressed somatic missense mutations are translated into pairs of short peptide strings: one including the mutation and one corresponding to the wild-type sequence. Next, in silico analysis is performed using NetMHC (<http://www.cbs.dtu.dk/services/NetMHC-3.2/> (32, 44)) to predict the binding affinity of a given peptide for patient-specific MHC I. IEDB (<http://www.iedb.org> (33)) is also used to predict the induction of a T-cell response to a given amino acid peptide sequences. Candidate neoantigens will be identified by having high predicted MHC binding affinity (<50nM), significantly greater affinity than their WT counterpart, and having the capacity to induce a T-cell response.

The binding affinity of a given candidate neoantigen is dependent in part on the specific MHC I and II alleles that are presenting the antigen. Although initial studies restricted analysis to the predicted binding affinity to HLA-A\*02:01 (45), the most common allele in Caucasians, NetMHC 3.2 is now able to predict the nanomolar peptide binding affinity of nearly any human HLA allele (46). Exome sequencing done above may not provide sufficient coverage to accurately determine the patient-specific HLA allele, so HLA typing will be performed separately using normal DNA.

Due the rapid improvement of bioinformatics tools, the details of the analytical plan described above is subject to change.

#### **14.1.3.2 Study 2: Characterization of Tumor Markers, Gene Expression, Infiltrating Lymphocytes and Circulating Lymphocytes (Wolchok Laboratory, MSKCC)**

PBMCs will be obtained at various time points coinciding with patient visits for clinical assessments (Arm 1: baseline, Weeks 1, 3, 5, 9, 11, 13; End of Treatment; progression, withdrawal or removal from study) (Arm 2: baseline, Weeks 1, 4, 7, 10, 14, 16; End of Treatment; progression, withdrawal or removal from study). Tumor samples from baseline (archived specimen or fresh biopsy) and Week 6 (fresh biopsy) will be obtained.

**PBMC Processing will be performed by the Alliance Biorepository at Ohio State University.**

#### **Recommended PBMC preparation protocol:**

PBMC processing will be performed by Alliance Biorepository at Ohio State University. Centrifuge for 20 minutes at 1700 x g. If after centrifugation the upper phase above the gel is not clear of RBCs, the tube should be centrifuged for an additional 15 minutes. After centrifugation, the PBMCs will be found in a diffuse, whitish layer above the gel or on the sides of the tube. Without disturbing the cell layer, use a transfer pipette to remove approximately half the upper clear plasma layer (~3 mL). With a clean transfer pipette, gently pipette the remaining plasma and cells up and down to dislodge any cells that may be resting on the gel layer, or the sides of the tube. Transfer the cell suspension to a 15 mL conical tube. Add room temperature

RPMI-10 to the conical tube to a final volume of 13 mL, cap the tube tightly, and mix by gentle inversion. Centrifuge at  $250 \times g$  for 15 min at room temperature. The supernatant may be cloudy. These are platelets above the cell pellet. Decant or aspirate the supernatant without disturbing the cell pellet. Flick the tube to resuspend cells. Repeat washing steps (RPMI-10, suspension, centrifuge, decant supernatant) 1-2 more times. While waiting for the 2nd (or 3rd) wash, fill an insulated ice pan with ice. After the 2nd (or 3rd) wash is complete, remove a small aliquot to record the cell count and viability, then place tube on ice. For each timepoint, collect the following parameters:

- i. Cell viability (%) before freezing
- ii. Total yield of PBMCs ( $\times 10^6$  cells/mL/vial) isolated prior to freezing

Prepare a freezing container (e.g. Nalgene cat #5100-0001 or equivalent) Remove the high-density polyethylene vial holder and foam insert from the Nalgene Freezing Container. Do not discard the foam insert. Container must be at room temperature prior to use. Do not pre-chill. Add approximately 250 mL of 100% isopropyl alcohol to the fill line on the Freezing Container. Do not overfill. Carefully replace the foam insert and vial holder in the Freezing Container.

To freeze the PBMCs: Important to Note: PBMC Freezing media contains DMSO, which is toxic to the cells if they are not frozen immediately after suspension in freezing media. Flick 15mL centrifuge tube containing the PBMC pellet to resuspend cells. Using a transfer pipette, quickly resuspend the pellet in 1 mL of COLD Freezing Medium.

- i. NOTE: Prepare media per the instructions contained inside the media kit box.
- ii. Mix the cells up-and-down a few times until well mixed (no visible clumps).
- iii. Immediately dispense the entire volume into the pre-labeled cryovial. Cap the vial tightly. Keep samples on ice until transferred to the Freezing Container. Aliquot PBMCs into provided labeled cryovials. A minimum of seven (7) cryovials should be obtained.
- iv. NOTE: Each cryovial should contain a minimum of  $5 \times 10^6$  cells/mL/vial and a maximum of  $15 \times 10^6$  cells/mL/vial. For each cryovial prepared, please record the total # of PBMCs in the cryovial.
- v. If there are less than 35 million cells, as many cryovials with 5 million cells should be made as possible.
- vi. Place sample vials in Freezing Container vial holder. Place the lid on the Freezing Container and place in a  $-70^{\circ}\text{C}/-80^{\circ}\text{C}$  freezer immediately. For each cryovial prepared, please record the date and time placed into the freezer.
- vii. NOTE: Leave undisturbed overnight or for a minimum of 12 hrs and a maximum of 24 hrs.

Transfer samples to liquid nitrogen storage freezer. Record the time, date, and location that the samples were placed in liquid nitrogen storage. For each cryovial prepared, please record the date and time placed into liquid nitrogen storage.

**Immunohistochemistry for PD-L1:** Immunohistochemical staining for PD-L1 (DAKO, Carpinteria, CA) will be performed on 5  $\mu\text{m}$  thick sections obtained from

formalin-fixed paraffin embedded tissue of the selected cases. PD-L1 positivity was defined as >1% of tumor cells (minimum of 100 evaluable cells) demonstrating plasma membrane staining. Macrophage and lymphocyte PD-L1 status will be determined qualitatively. Positive macrophage or lymphocyte PD-L1 expression inside and/or outside of the tumor expression will be defined.

Immunohistochemical staining for PD1 (mouse clone NAT antibody, LOT#GR81330-2 Abcam Cambridge, MA or equivalent

**Gene Expression:**

Fresh tumor biopsy will be examined for RNA gene expression by Affymetrix gene array technology and/or qRT-PCR to detect expression of immune related genes. Genes of interest include, but are not limited to PD-1, PD-L1, IDO2, Il-6, CTLA-4, KIR/KIR-ligand mismatch.

**Flow Cytometry:**

Markers including, but not limited to, activated (HLA-DR+) and memory (CD45RA-) T cells; CD4/CD25/FoxP3, CD4/CD8/CD45RA/CCR7, CD4/CD8/LAG3/PD-1/PD-L1, CD4/CD8/CD137 will be assessed utilizing MSKCC immune core facilities. The functional status of effector T cells will be assessed using assays such as interferon-gamma and granzyme B.

**14.1.3.3 Study 3: Serum/Plasma Cytokines**

Whole blood will be obtained at various time points coinciding with patient visits for clinical assessments (Arm 1: baseline, Weeks 1, 3, 5, 9, 11, 13; End of Treatment; progression, withdrawal or removal from protocol therapy) (Arm 2: baseline, Weeks 1, 4, 7, 10, 14, 16; End of Treatment; progression, withdrawal or removal from protocol therapy). Serum will be extracted by the Alliance Biorepository at Ohio State. Plasma isolated during PMBC preparation can substitute for serum when necessary. Multiplex ELISA assays for factors which may include but are not limited to IL-2, -4, -5, -6, -8, -10, -12, -17; CXCL9, CXCK10, and VEGF will be assessed at baseline and at various time points. Associations will be explored between these changes and degree of clinical benefit.

Considering the rapid improvement of biotechnology, more updated analytical tools and platforms may be used

**15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING**

There are no credentialing requirements for A091401.

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**APPENDIX I    REGISTRATION FATIGUE/UNISCALE ASSESSMENTS**

**Registration Fatigue/Uniscale Assessments**

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

## APPENDIX II CRADA

### Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

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

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

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

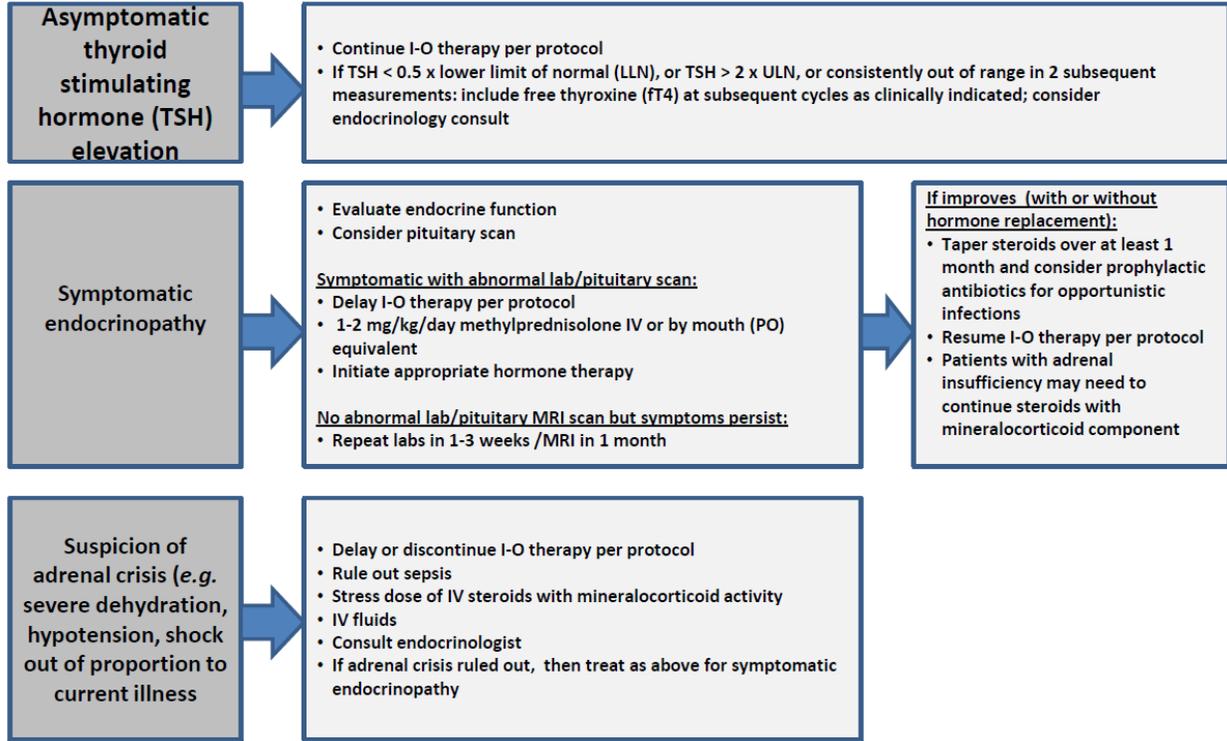
Email: [ncicteppubs@mail.nih.gov](mailto:ncicteppubs@mail.nih.gov)

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

APPENDIX III TOXICITY ALGORITHMS

## Endocrinopathy Management Algorithm

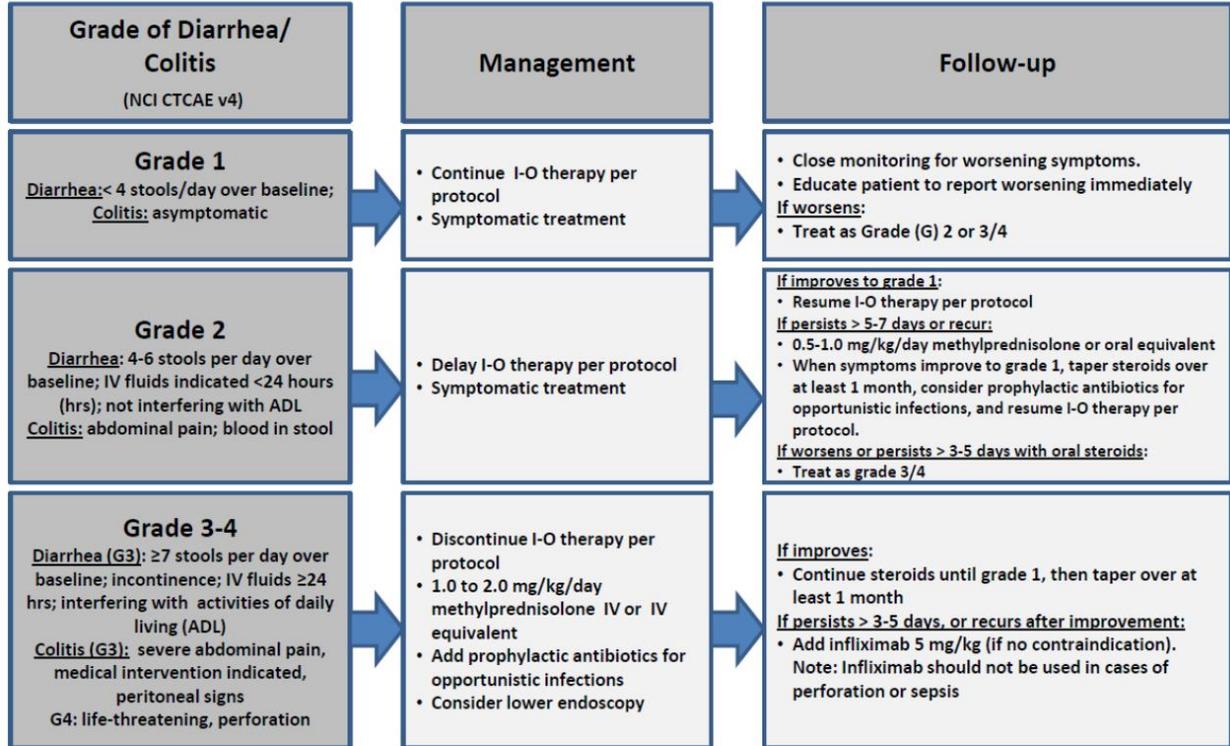
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

## GI Adverse Event Management Algorithm

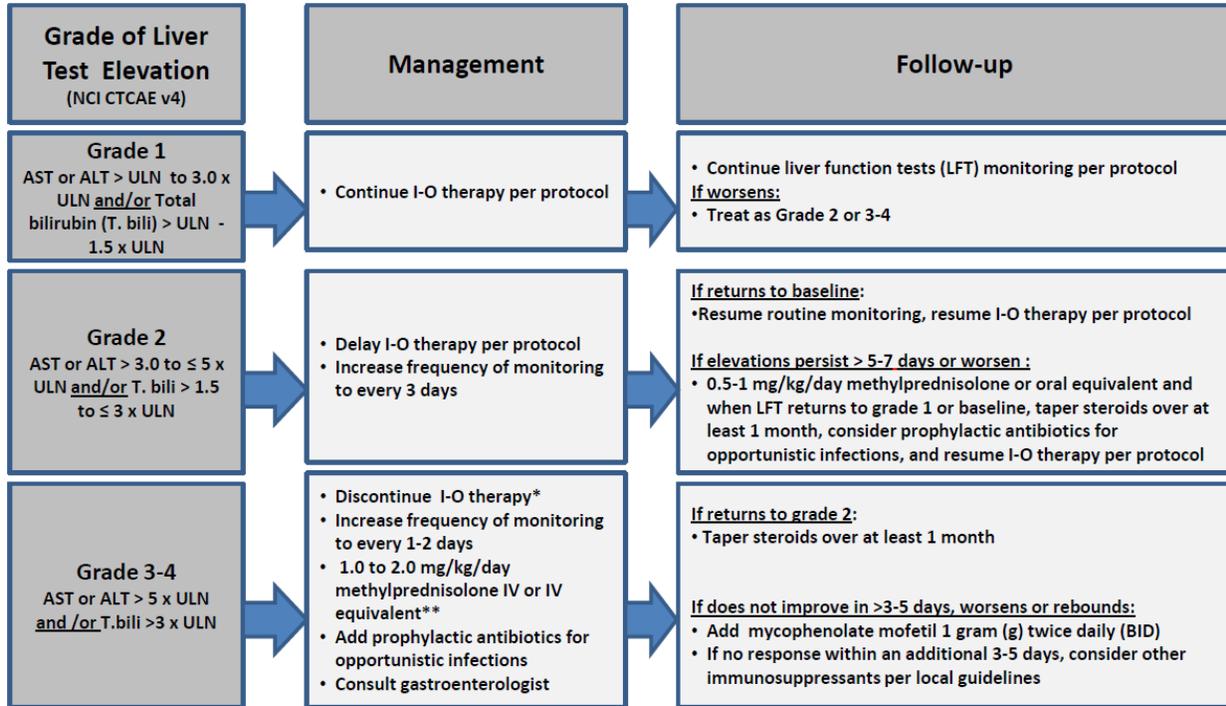
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

## 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.



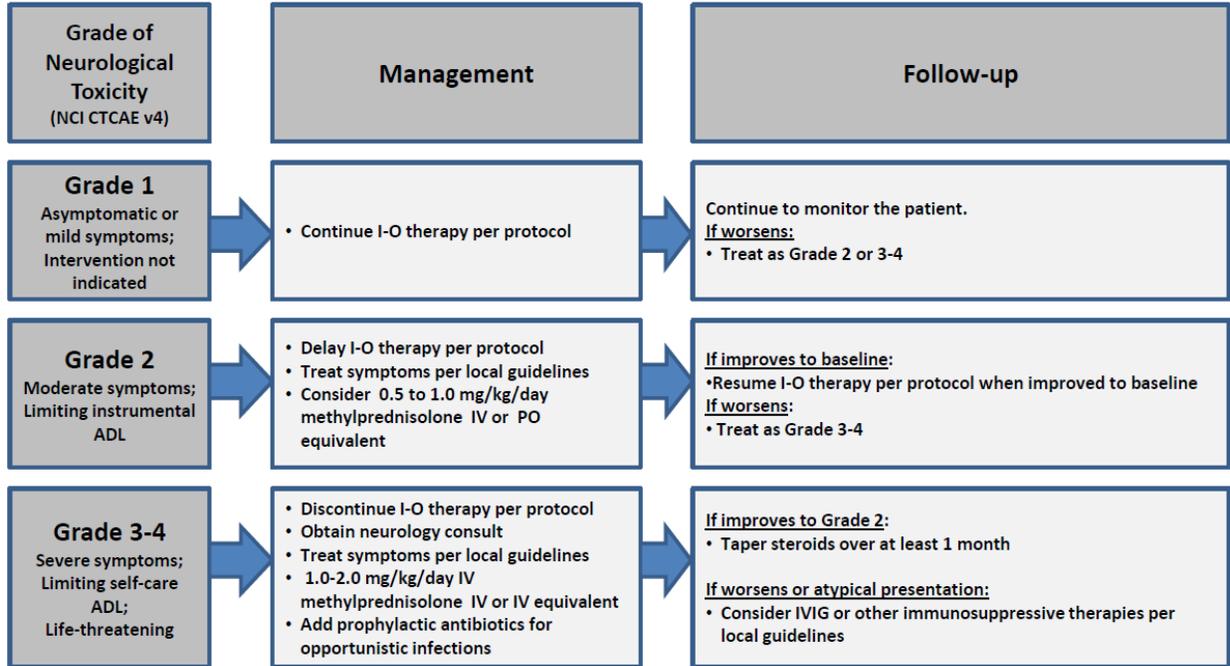
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

## Neurological Adverse Event Management Algorithm

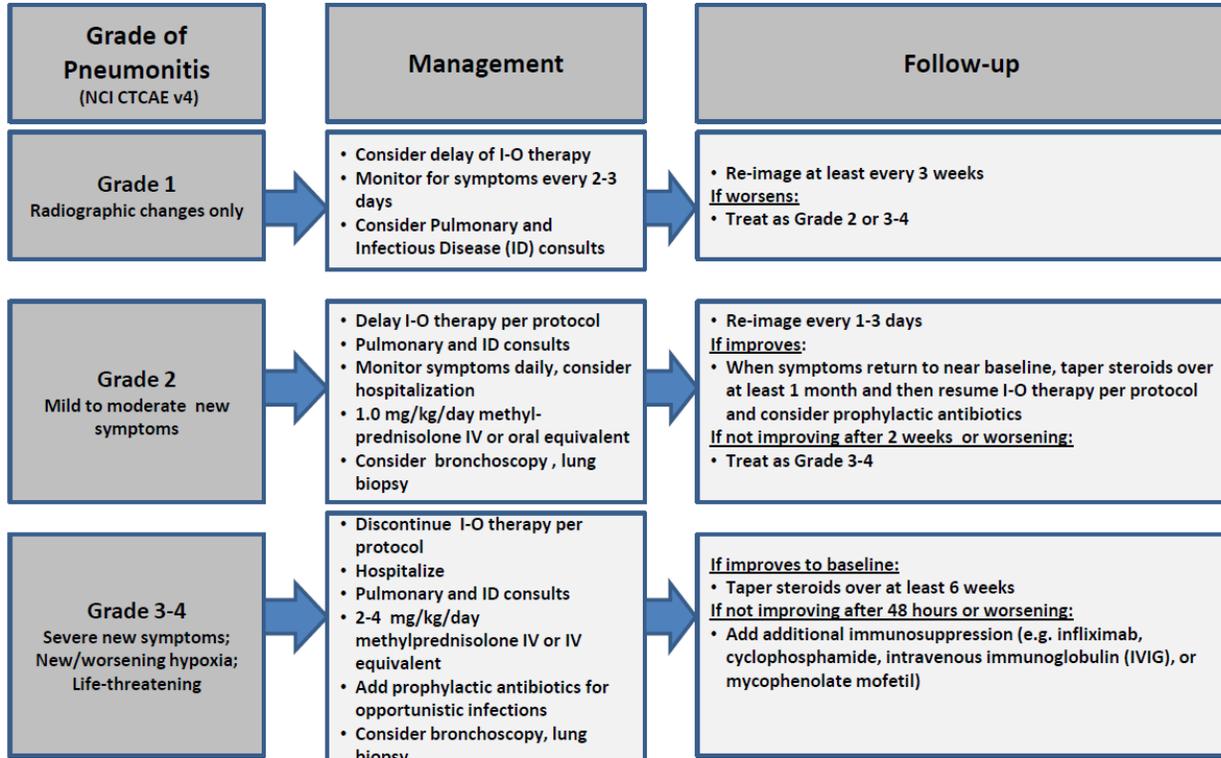
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

## Pulmonary Adverse Event Management Algorithm

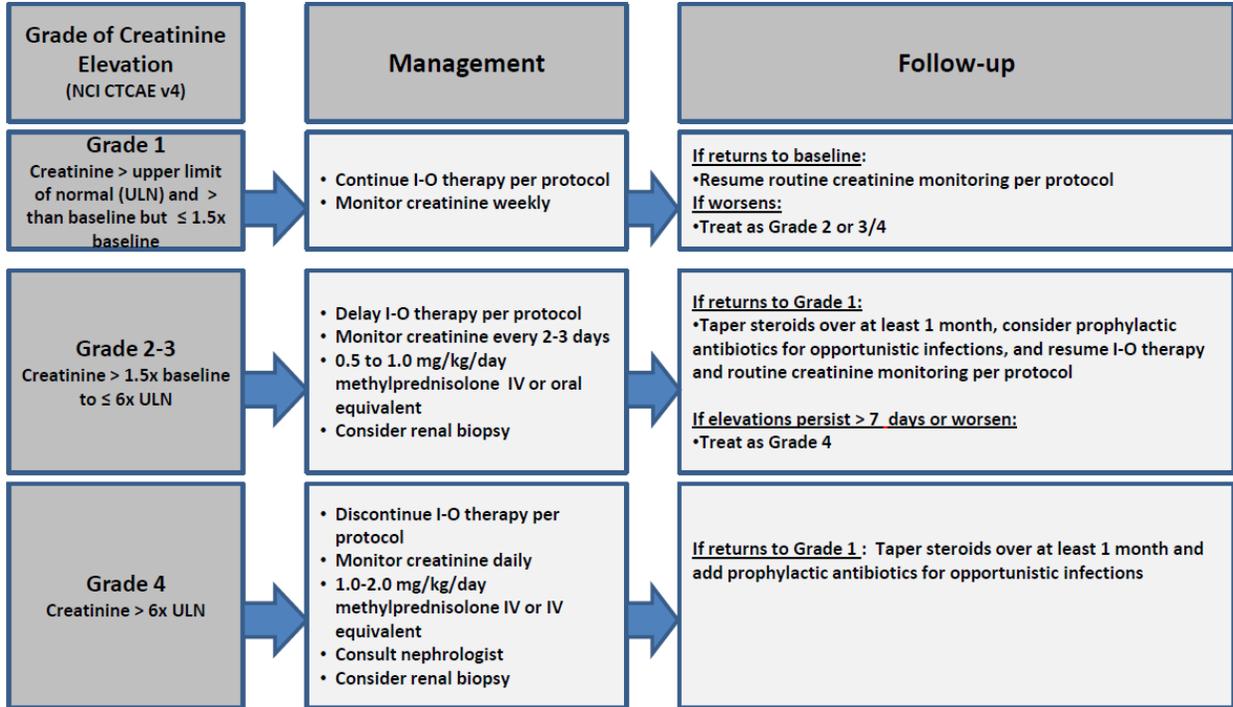
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

## Renal Adverse Event Management Algorithm

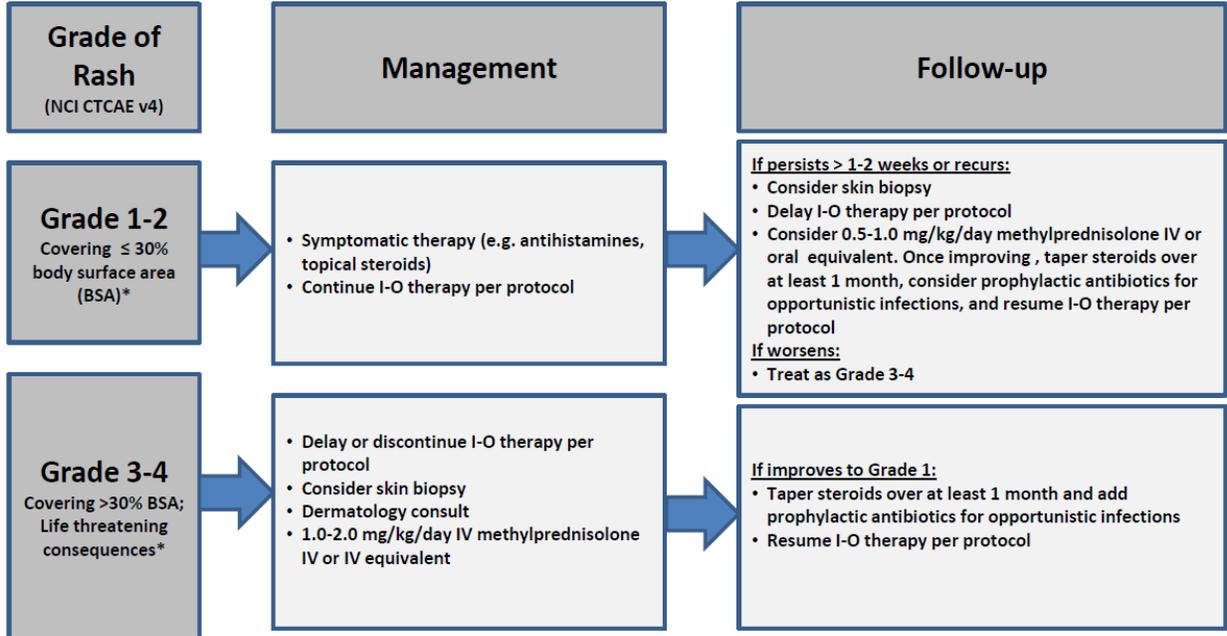
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

## Skin Adverse Event Management Algorithm

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



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.

\*Refer to NCI CTCAE v4 for term-specific grading criteria.

#### **APPENDIX IV DEFINITION OF ACTIVE AUTOIMMUNE DISEASE**

Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, polymyositis, rhabdomyolysis, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible.

Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome, vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, psoriasis controlled with topical medication, or conditions not expected to recur in the absence of an external trigger (precipitating event).and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

**APPENDIX V MANAGEMENT OF INFUSION REACTIONS**

All infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4.0 guidelines.

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

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

Monitor subject continuously until recovery from symptoms. Infusion rate may be slowed. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

**For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

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

**For Grade 3 or Grade 4 symptoms:**

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

**Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).**

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., fever, hypotension, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given

(e.g., oral antihistamine, or corticosteroids). Note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation (e.g. hepatitis, hypophysitis, colitis) associated with treatment. Please evaluate accordingly.