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Kimmel Cancer Center

Ipilimumab and Nivolumab in Combination with Immunoembolization for the Treatment of Metastatic Uveal Melanoma

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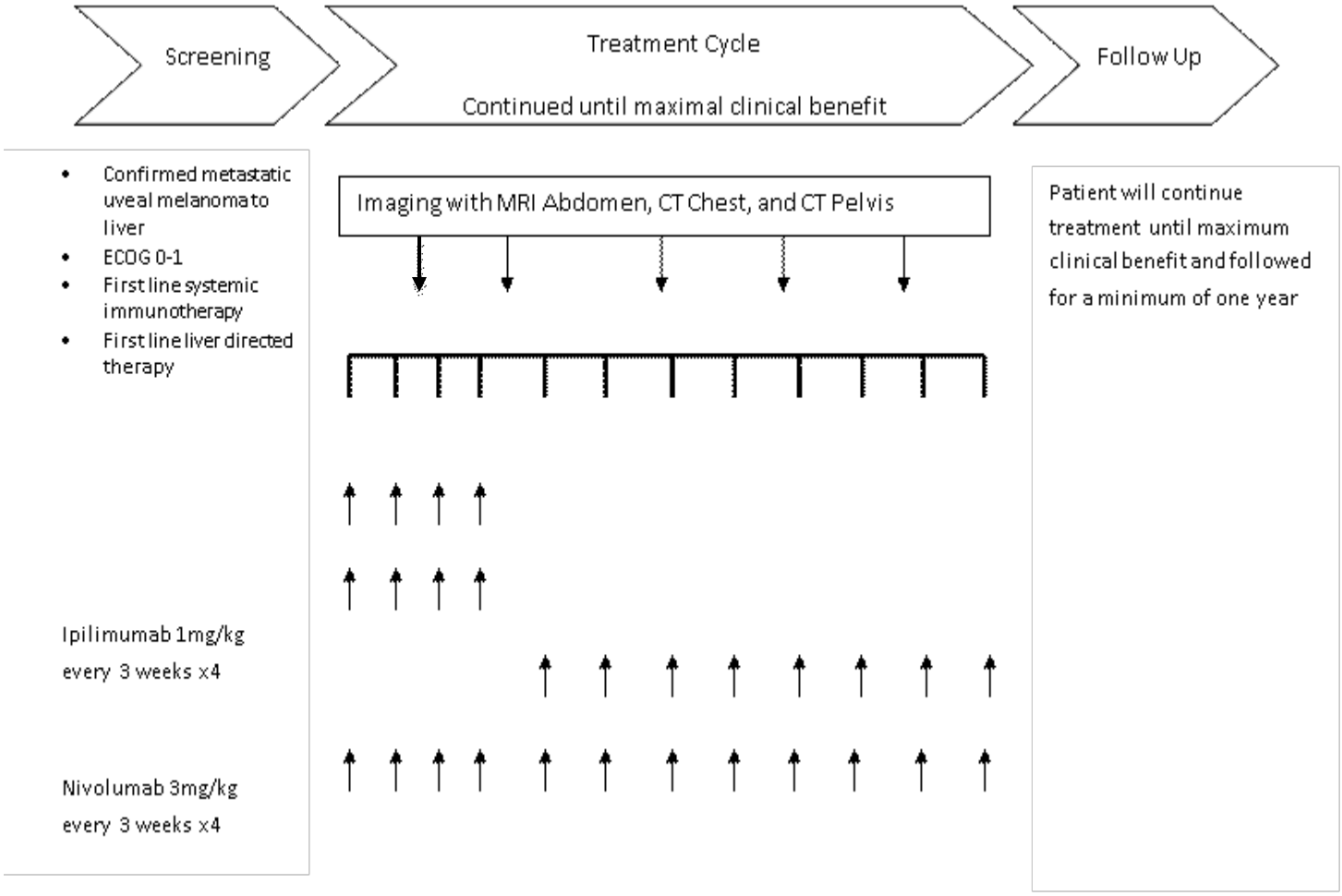
Study Summary

Title	Ipilimumab and Nivolumab in Combination with Immunoembolization for the Treatment of Metastatic Uveal Melanoma
Lay Title	A research study to investigate whether closure of the liver artery after injection of GM-CSF in combination with ipilimumab and nivolumab stops the growth of secondary liver tumors from primary uveal melanoma
BMS Protocol Number	CA209-9CH
Phase	Phase II
Methodology/Study Design	Open label, prospective, Phase II single arm trial. Patients will receive immunoembolization (IEMBO) every 3 weeks in combination with ipilimumab (IPI)+ nivolmuab (NIVO) initially to be given every 3 weeks for 4 doses. Dose of IPI + NIVO will be the reverse lower dose of IPI 1mg/kg every 3 weeks x4 doses and NIVO 3mg/kg every 3 weeks x 4 doses then NIVO flat dose 480mg every 4 weeks. In the event of toxicity during the first four IPI + NIVO + IEMBO combination treatments, IPI and/or NIVO may be dropped at the investigator's discretion and patient can continue on with NIVO + IEMBO or IEMBO alone. Once patient completes the first four doses of combination and moves onto the maintenance NIVO phase, IEMBO will then be given every 4 weeks. In the event of NIVO-related toxicity during this phase, NIVO can be dropped at the investigator's discretion. Initial scans will be performed following two IPI+NIVO and IEMBO treatments, before treatment #3, to ensure no evidence of rapid progression. Initial radiographic response will be determined following all 4 doses of IPI+NIVO and/or NIVO alone if IPI dropped and/or four IEMBO treatments if both IPI and NIVO are dropped. Subsequent scans will be done every two IEMBO treatments. Immune-related side effects will be managed as per protocol. Steroid treatment will be allowed if it is tapered to 5 mg of prednisone or less before initiation of next cycle. Combination treatment could be postponed for up to 10 weeks (from the date of next scheduled treatment). if patients need a treatment break for immune-related toxicity. Safety will also be assessed and the toxicity of the treatment will be monitored using the NCI Common Toxicity Criteria. Immunologic parameters will also be evaluated as detailed in the protocol.
Study Duration	18-24 months to accrue. Subjects will receive study treatment for a maximum of 2 years and will subsequently be followed for a minimum of one year.
Study Center(s)	Thomas Jefferson University Hospital

Objectives	**Primary Objective:** Determine the clinical benefit of combination treatment with IEMBO, Ipilimumab, and Nivolumab. **Secondary Objective(s):** 1. Determine all treatment and immune related toxicities 2. Determine PFS 3. Determine OS **Exploratory Objective:** 1. Determine and correlate clinical response with the degree and change in inflammatory/immune response
Number of Subjects	35
Diagnosis and Main Inclusion Criteria	**<u>Inclusion criteria:</u>** 1. Histologically confirmed metastatic uveal melanoma in the liver. Patients must have at least one measurable liver metastasis that is ≥ 10 mm in longest diameter by CT scan or MRI. The total volume of the tumors must be less than 50% of the liver volume. 2. Willingness and ability to give informed consent. 3. ECOG performance status of 0, or 1 4. Adequate renal and bone marrow functions: serum creatinine ≤ 2.0 mg/dl, granulocyte count ≥ 1000/mm3, and platelet count ≥ 100,000/mm3. 5. Adequate liver function: bilirubin ≤ 2.0 mg/ml, albumin ≥ 3.0 g/dl, PT/PTT less than 1.5 times of upper normal limit (UNL), and AST and ALT less than 3.0 and alkaline phosphatase less than 1.5 times of UNL. 6. Age ≥ 18 years of age.
Study Therapy, Dose, Route, Regimen	1. Recombinant human GM-CSF (Sargramostim, Leukine®, Sanofi US). GM-CSF 1,500 mcg) will be mixed with ethiodized oil (Ethiodol®). The GM-CSF/ethiodized oil mixture will be injected selectively into one of the hepatic lobes. This will be followed by infusion of gelatin sponge particles to achieve the stasis of blood flow (**immunoembolization**). This will repeat every 3 weeks x 4 then every 4 weeks 2. Ipilimumab (Yervoy) at 1mg/kg every 3 weeks x 4 doses. 3. Nivolumab (Opdivo) at 3mg/kg every 3 weeks x 4, then flat dose 480mg every 4 weeks.
Duration of administration and follow-up	Patients will receive combination treatment of immunoembolization, ipilimumab, and nivolumab every 3 weeks for 12 weeks and in patients with CR, PR, and SD at 12 weeks, maintenance therapy with combination immunoembolization and nivolumab every 4 weeks will be offered until disease progression or unacceptable toxicity, for a maximum of 2 years. Follow-up contact will take place every 3 months for minimum of one year or until death to determine clinical status.

Statistical Methodology	We propose an increase in hepatic metastasis stabilization rate (SD+PR+CR) of 60%, as experienced with IEMBO alone, to 80% with IEMBO + IPI + NIVO. We plan to enroll 35 patients to have a power > 80% (alpha = 0.05) and to detect our proposed response rate. Simon's two-stage design will be used (Minimax). The null hypothesis that the true response rate is 60% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are 8 or fewer responses in these 13 patients, the study will be stopped. Otherwise, 22 additional patients will be accrued for a total of 35. The null hypothesis will be rejected if 26 or more responses are observed in 35 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 80%.

Study Schema



1.0 INTRODUCTION

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

1.1 Background and Rationale

Uveal melanoma is the most common primary intraocular cancer in adults. Incidence in the United States is four to seven per million people and noted to make up approximately 3% of all melanomas.[1] Despite the availability of effective treatments for primary uveal melanoma, there is no standard adjuvant therapy and up to 50% of patients subsequently develop metastasis.[1] Hepatic involvement is often the first manifestation of systemic disease, and in more than half of patients it remains the only site of metastases. Other sites of metastases include lungs, bones, brain, subcutaneous tissues, peritoneal cavity, and other visceral organs. Survival after liver metastases is reportedly less than 6 months without treatment.

The major challenge in management of metastatic uveal melanoma is the lack of effective treatments. Metastatic uveal melanoma is highly resistant to standard systemic chemotherapies that have been used for metastatic skin melanoma.[2] A novel approach using a MEK inhibitor showed a modest but improved response (15% RECIST response) in metastatic uveal melanoma.[3] However, the progression free survival was short (15.9 weeks) and there was no significant overall survival benefit.

Over the past decade, there have been paradigm-altering advances in cutaneous melanoma due to the advent of effective systemic immunotherapy interventions including immune-checkpoint-pathway blockades such as anti–CTLA-4 antibody (ipilimumab) and anti–PD-1 antibody (pembrolizumab and nivolumab).[4] Despite encouraging clinical study results in metastatic cutaneous melanoma, these immune checkpoint blockades have not shown dramatic response in metastatic uveal melanoma. Ipilimumab resulted in regression in only 5% of metastatic uveal melanoma patients.[5,6] On the other hand, toxicity to ipilimumab, especially immune-related toxicity, is considered to be similar to that of metastatic skin melanoma (~30% grade 3 or greater). Published data now for anti-PD1 and anti-PDL1 antibodies when used alone note an approximate 3.6% response rate and 9% stable disease rate.[7]

Since the liver is usually the dominant site of metastasis and hepatic metastasis is life-limiting in the majority of uveal melanoma patients, liver-targeted locoregional treatment is a preferred standard of care since there are no effective systemic treatments available at this time.[8] Considering resistance to standard chemotherapeutic treatment, we have developed a new therapy called Immunoembolization (IEMBO)[9-11]. This technique involves embolization of the hepatic artery with gelatin sponge particle in conjunction with administration of granulocyte-macrophage colony stimulating factor (GM-CSF) mixed with ethiodized oil through the tumor-feeding hepatic artery. IEMBO provides several advantages beyond the ischemic damage consequent to bland embolization alone. Some of these advantages include attraction and stimulation of antigen-presenting cells in the hepatic tumor sites and improved uptake of tumor antigens released from necrotic tumor cells. In addition, local stimulation of the immune system may produce a systemic immune response against tumor cells, which thereby suppresses the growth of extrahepatic metastases.[11] This

approach resulted in stabilization of multiple hepatic metastasis in approximately 60% of uveal melanoma patients. Furthermore, this liver-directed treatment induced a systemic response against melanoma, including the development of inflammatory responses in remote metastasis and the prolongation of progression-free survival in extra-hepatic metastasis.[9-11]

Due to the low response rate of systemic single agent immune checkpoint inhibitor therapy in metastatic uveal melanoma, we have been combining with IEMBO with systemic ipilimumab as well as pembrolizumab and nivolumab as our institutional standard of care. It is hypothesized that inflammation induced by IEMBO with GM-CSF coupled with systemic immune checkpoint therapy could be synergistic. We have published on our experience with combination IEMBO and ipilimumab.[12] The combination was well tolerated and incidence of serious hepatic toxicity was low. Our experience with IEMBO in combination with anti-PD1 antibodies has been similar.

In cutaneous melanoma the combination of Ipilimumab and Nivolumab over each agent alone has proven to result in improved response rate and deeper responses.[13] While we do not have data regarding this combination in metastatic uveal melanoma, there is reason to believe that the combination may prove also to be superior to each agent when used alone.

To further enhance local and systemic anti-tumor immune responses, we proposed to investigate the safety and efficacy of IEMBO + Ipilimumab + Nivolumab combination treatment.

2.0 STUDY OBJECTIVES

2.1 Primary Objective: Determine the clinical benefit of combination treatment with IEMBO in combination with Ipilimumab and Nivolumab.

2.2 Secondary Objective:

a. Determine all treatment and immune related toxicities
b. Determine progression free survival
c. Determine overall survival

2.3 Exploratory Objective:

a. Determine and correlate clinical response with the degree and change in inflammatory/immune responses

3.0 STUDY DESIGN

3.1 General Design

This study is an open label, prospective, phase II, two-stage, single arm trial with the potential for improved outcome with treatment of IEMBO in combination with IPI + NIVO. Patients will receive study treatment for a maximum of two years or until disease progression. The design will be a two-stage minimax design using the method of Simon. Choice of design is guided by a desire to stop the trial early if the actual hepatic metastasis stabilization rate is 60% or less. If the stabilization rate rate is 80% or greater, we would like to have a low probability of failing to conclude effective.

Patients will receive IEMBO every 3 weeks in combination with IPI + NIVO initially to be given every 3 weeks for 4 doses. Dose of IPI + NIVO will be the reverse lower dose of IPI 1mg/kg every 3 weeks x4 doses and NIVO 3mg/kg every 3 weeks x 4 doses then NIVO flat dose 480mg every 4 weeks. In the event of toxicity during the first four IPI + NIVO + IEMBO, IPI and/or NIVO may be dropped at the investigator's discretion and patient can continue on with NIVO + IEMBO or IEMBO alone. Once patient completes the first four doses of combination and moves onto the maintenance NIVO phase, IEMBO will then be given every 4 weeks. In the event of NIVO-related toxicity during this phase, NIVO may be dropped at the investigator's discretion and the patient may continue on with IEMBO only, if the investigator feels patient is receiving clinical benefit from it. Initial scans will be performed between cycles 2 and 3 to ensure no evidence of rapid progression. Initial radiographic response will be determined following all 4 doses of IPI+NIVO and/or NIVO alone if IPI dropped,and/or four IEMBO treatments if both IPI and NIVO are dropped. Subsequent scans will be done after every two IEMBO treatments. Immune-related side effects will be managed as per protocol. Steroid treatment will be allowed if it is tapered to 5 mg of prednisone or less before initiation of next cycle. Combination treatment could be postponed for up to 10 weeks (from the date of next scheduled treatment), if patients need a treatment break for immune-related toxicity. Safety will also be assessed and the toxicity of the treatment will be monitored using the NCI Common Toxicity Criteria. Immunologic parameters will also be evaluated as detailed in the protocol.

3.2 Primary Study Endpoint

1. Best hepatic response (CR + PR +SD) by response criteria (RECIST 1.1) starting at week 12

3.3 Secondary Study Endpoints

1. All toxicities using the NCI CTCAE Version 4.0.
2. Progression Free Survival (hepatic and systemic PFS)
3. Overall survival

3.4 Exploratory (Correlative) Endpoints

Systemic and local immune/inflammatory response:

a. Degree and classification of tumor-infiltrating cells
b. Presence and changes in PD-L1 expression in tumor and tumor-infiltrating cells
c. Changes in immune tumor microenvironment (immune gene signature)
d. Tumor mutational burden prior to treatment
e. Changes in TCR repertoire analysis (ImmunoSeq)
f. Changes in cytokine productions (multiplex cytokine assay)
g. Changes in PBMC cell populations, including T cells and MDS.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

1. Histologically confirmed metastatic uveal melanoma in the liver. Patients must have at least one measurable liver metastasis that is ≥ 10 mm in longest diameter by CT scan or MRI.
2. The total volume of the tumors must be less than 50% of the liver volume.
3. Willingness and ability to give informed consent.
4. Agreement to access archival tissue or agreement for tumor biopsy prior to treatment
5. ECOG performance status of 0, or 1
6. Adequate renal and bone marrow functions: serum creatinine ≤ 2.0 mg/dl, granulocyte count ≥ 1000/mm3, and platelet count ≥ 100,000/mm3.
7. Adequate liver function: bilirubin ≤ 2.0 mg/ml, albumin ≥ 3.0 g/dl, PT/PTT less than 1.5 times normal, AST and ALT less than 3x ULN and alkaline phosphatase less than 1.5 times ULN (grade 1).
8. Age ≥ 18 years of age.
9. Women must not be pregnant or breast-feeding. See section 4.2.1
10. Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 23 weeks after the last dose of nivolumab and/or ipilimumab and sexually active males must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 31 weeks after the last dose of nivolumab and/or ipilimumab. See section 4.2.1

4.2 Exclusion Criteria

1. Failure to meet any of the criteria set forth in the Inclusion criteria section
2. Previous systemic exposure to anti-CTLA-4 antibody or anti-PD1 antibody
3. Previous liver-directed treatments including chemoembolization, radiosphere, hepatic arterial perfusion, or drug-eluting beads; liver resection and focal ablation are permitted.
4. Presence of symptomatic liver failure including ascites and hepatic encephalopathy.
5. Presence of untreated brain metastases. If patients have had previous treatment for the brain metastasis, an MRI or CT scan of the brain must confirm the stabilization of the brain metastasis for more than 2 months.
6. Presence of uncontrolled hypertension or congestive heart failure, or acute myocardial infarction within 6 months of entry.
7. Presence of any other medical complication that implies survival of less than six months
8. Uncontrolled severe bleeding tendency or active GI bleeding.
9. Significant allergic reaction to contrast dye or GM-CSF.
10. Immunosuppressive treatments within 4 weeks prior to embolization, unless prednisone ≤ 5mg or equivalent
11. Pregnancy or breast-feeding women.
12. Patients with active hepatitis with SGOT and SGPT equal or greater than 5 times normal
13. Biliary obstruction, biliary stent or prior biliary surgery except cholecystectomy
14. Positive for known HIV Infection

15. Uncontrolled Chronic Obstructive Pulmonary Disease or previous known pulmonary fibrosis
16. Active infection.
17. Auto-immune disease including inflammatory bowel disease, lupus, rheumatoid arthritis, but not including hypothyroidism or psoriasis if condition has been stable for 2 months or greater.

4.2.1 Guidance for Women of Child Bearing Potential

Women must not be pregnant or breast-feeding. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to start of treatment to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Women of child-bearing potential must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 23 weeks after the last dose of nivolumab and/or ipilimumab and sexually active males must use at least two other accepted and effective methods of contraception and/or to abstain from sexual intercourse for at least 31 weeks after the last dose of nivolumab and/or ipilimumab. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

4.3 Early Withdrawal of Subjects

4.3.1 When to Withdraw Subjects

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdraw of consent or lost to follow up.
2. Subject is determined to have met one or more of the exclusion criteria and continuing therapy may be a safety risk
3. Pregnancy or intent to become pregnant
4. Any adverse event that meets criteria for discontinuation
5. Subject non-compliance that in the opinion of the investigator or sponsor warrants withdrawal
6. Initiation of alternative anti-cancer therapy
7. Confirmation of progression of disease

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who are withdrawn from the study and permanently discontinued from receiving on study treatment will be followed for safety, including the collection of any protocol-specified blood specimens, unless consent if withdrawn or the subject is lost to follow up or enrolled in another clinical trial. All subjects will be followed for survival. Any subjects who are unable to return to the site for visits will be offered to follow up by phone every three months for at least one year.

4.3.3 Replacement of Subjects

Should a subject be withdrawn from the study prior to the assessment at the fourth cycle for any other reason besides clinical deterioration or toxicity they will be replaced as they will not be evaluable.

5.0 STUDY DRUG/THERAPY

- GM-CSF, Ethiodol, and Gelatin Sponge as part of IEMBO will be given as standard of care in this study.
- Ipilimumab and Nivolumab will be given as investigational in this study.

5.1 Drug Descriptions/Formulation/Procurement

Receipt of Study Drug Supplies [ipilimumab and nivolumab]

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.1.1 GM-CSF (yeast-derived recombinant human GM-CSF)

- Other Names; Leukine®, Sargramostim
- Classification: Hematopoietic growth factor
- Mode of Action: Stimulates proliferation and differentiation of hematopoietic progenitor cells. Increases the cytotoxicity of monocytes toward certain neoplastic cell lines and activates polymorphonuclear neutrophils to inhibit the growth of tumor cells (41).
- Storage and stability: Leukine Liquid (500 mcg/ml) will be refrigerated at 2-8 ^{o}C until use. The Leukine Liquid may be stored for up to 20 days at 2-8 ^{o}C once the vial has been entered.
- Preparation: Three vials of Leukine Liquid (500 mcg) will be used to make a 2,000 mcg GM-CSF solution in 4 ml.
- Side Effects: In uncontrolled Phase I/II studies with Leukine® in 215 patients, the most frequent adverse events were fever, asthenia, headache, bone pain, chills and myalgia (>10%). These systemic events were generally mild or moderate and were usually prevented or reversed by the administration of analgesics and antipyretics such as acetaminophen. In these uncontrolled trials, other infrequent events reported were dyspnea, peripheral edema, and rash.
    - Reports of events occurring with marketed Leukine® include arrhythmia, fainting, eosinophilia, dizziness, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities (<1% occurrence post-marketing).
    - In patients with preexisting edema, capillary leak syndrome, pleural and/or pericardial effusion, administration of Leukine® may aggravate fluid retention. Body weight and hydration status should be carefully monitored during Leukine® administration. Occurred 1% patients.

- In patients with preexisting liver or renal insufficiency, increased creatinine or bilirubin and hepatic enzymes would be observed. Transient increase of WBC counts may develop after the local infusion of GM-CSF into hepatic artery.
- Rarely, patients have developed acute allergic reactions or hemiplegia (<1% occurence).

5.1.2 Ethiodized Oil

- Other Names; Ethiodol®
- Classification; Injectable radio-opaque diagnostic agent
- Drug specifics: Ethiodol®, brand of ethiodized oil, is a sterile injectable radio-opaque diagnostic agent for use in hysterosalpingography and lymphography. It contains 37 % iodine (475 mg/ml) organically combined with ethyl esters of fatty acids (primarily as ethyl monoiodostearate and ethyl diiodostearate) of poppyseed oil. Ethiodized oil has been used widely for chemoembolization of the hepatic artery for primary and metastatic liver cancer.
- Side Effects: One of the major side effects of ethiodized oil is impairment of liver function (38). Since ethiodized oil causes ischemic changes in the liver, special attention to liver function should be considered. Visualization of the portal vein is a sign of portal reflux through sinusoids. Infusion of ethiodized oil should be stopped if the larger order portal vein branches are visualized. Another rare complication is pulmonary oil embolization, which is also seen when more than 20 ml of ethiodized oil is infused (50). In this study, the maximum dose of ethiodized oil for embolization will be 20 ml or less. Erosive gastroduodenal lesions or ischemic change in biliary ducts were reported in patients who received chemoembolization (51, 52). However, most of them are clinically insignificant and managed medically.

5.1.3 Gelatin sponge

- Other Names; Gelfoam®, Surgifoam®
- Classification; Medical device for hemostasis
- Drug specifics: Absorbable gelatin sponge is a medical device intended for application to bleeding surface as a hemostatic. It is a sterile, water-insoluble, non-elastic, pliable product prepared from purified porcine skin gelatin. Gelatin sponge is usually absorbed completely in from four to six weeks, without inducing excessive scar tissues.
- Side Effects: When gelatin sponge was used during intravascular catheterization for the purpose of producing vessel occlusion, the following adverse events have been reported; fever, necrosis of specific anatomical areas, duodenal and pancreatic infarcts and abscess. Since smaller sizes of the occlusive agents cause more ischemic complications and development of collateral circulation, gelatin sponge powder will not be used in this study.

5.1.4 Ipilimumab: In this study, ipilimumab is considered investigational.

- Other Names: Anti-CTLA-4 monoclonal antibody, MDX-010 (MDX-CTLA4, Transfectoma-derived), Yervoy®
- Classification: Human monoclonal antibody, IgG1 subclass
- Mode of Action: Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells and regulatory T cells. CTLA4 interaction with the B7 molecule,

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

- Storage and Stability - Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature between 2°C to 8°C. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 2 mg/mL. Undiluted or diluted ipilimumab solution is stable in a polyvinyl chloride (PVC), non- PVC/non DEHP (di-(2-ethylhexul) phthalate) IV bag or glass container up to 24 hours refrigerated at (2°C to 8°C) or at room temperature/ room light. Do not freeze. Shelf-life surveillance of the intact vials is ongoing.
- **CAUTION:** Ipilimumab does not contain antibacterial preservatives. Vials are for single use only. Use prepared IV solution immediately. Discard partially used vials.
- Dose Specifics Calculate Total Dose as follows: Patient body weight in kg x 1 mg/kg = total dose in mg
- Preparation: The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an intravenous infusion using an in-line filter (pore size of 0.2 micrometer to 1.2 micrometer) and a volumetric pump, at 1 mg/kg dose, to complete the infusion in 30 minutes, with a 3-mL normal saline flush at the completion of the infusion. Reduced duration of infusion as compared to the 90 minutes for 3mg/kg dosing was approved by BMS.
- As ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
- Mix by GENTLY inverting several times. DO NOT shake.
- Route of Administration: Ipilimumab is administered as an IV infusion only. Infusions should be administered over 30 minutes +/- 5 minutes. Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents.
- Incompatibilities: No compatibility information is available.
- Availability: Ipilimumab is available in 5 mg/mL single-use vials (40 mL). The sterile solution in the vial is clear and colorless.
- Side Effects: See the BMS Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 6.2 for list of side effects
- Nursing/Patient Implications: Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes. Ipilimumab may be excreted in milk or cross the placenta; therefore, nursing women and women with known or suspected pregnancy should not take ipilimumab. Closely monitor patients who are on narcotics during the treatment with ipilimumab. Narcotics may mask GI signs and symptoms such as diarrhea or abdominal pain, which are relevant complications of a bowel perforation. Minor diarrhea can be a potential sign of colitis and require immediate attention.
- Handling and Disposal: As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the

safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

- Ipilimumab Destruction: Partial vials can be destroyed on site per institution policy. Intact vials of the expired drug, recalled, or when protocol is closed to treatment cannot be destroyed on site without the PMB/NCI approval. If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

5.1.5 Nivolumab (NSC748726): In this study, nivolumab is considered investigational.

- Other Names: BMS-936558; MDX1106; ONO-4538; anti-PD-1
- Classification: Fully humanized monoclonal antibody
- Mode of Action: Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that targets the programmed death – 1 (PD-1) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its predominant ligand, PD-L1, results in the down regulation of lymphocyte activation. Loss of effective immune response to antigens expressed by tumors may be a significant factor in tumor progression. PD-L1 expression has been found on a number of tumors & may also be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response. Inhibition of PD-1 interaction with PD-L1 promotes immune responses and antigen specific T cell responses to both foreign antigens as well as self-antigens. Nivolumab was shown to promote the proliferation of human T-cells in a variety of assays, which is an anticipated pharmacologic result of PD-1 inhibition.
- Storage and Stability: Intact vials: 2-8°C (36-46°F); Protect from light, protect from freezing; Infusion – room temp: 4 hours max including infusion and up to 24 hours if refrigerated for the first 20 hours.
- Dose Specifics:The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.
- Preparation: Nivolumab is available as 100 mg vials (10 mg/mL), which include an overfill. It is supplied in 10 mL type I flint glass vials, with butyl stoppers and aluminum seals. Nivolumab injection can be infused diluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP to concentrations no less than 0.35 mg/mL.
- Route of Administration: IV using a volumetric pump with 0.22 micron pre size, low-protein binding polyethersulfone membrane in-line filter. Nivolumab should be administered over 30 minutes +/- 5 minutes. Should be administered ahead of ipilimumab on days when both to be administered
- Incompatibilities: No incompatibilities between Nivolumab injection and polyolefin bags have been observed.
- Side Effects: See the Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 6.2 for list of side effects.

- Nursing/Patient Implications: Infuse over 30 minutes +/- 5 minutes in a minimum of 60 ml infusion volume through a 0.22 micron in-line filter. Monitor carefully for infusion reactions and treat accordingly.
- Handling and Disposal: Use appropriate precaution for handling and disposal.

5.2 Dose Rationale

Patients will receive immunoembolization using GM-CSF at dose of 1500mcg every 3 weeks for the first four treatments then offered every 4 weeks maintenance. In the phase 1 dose escalation study, there was no dose-limiting toxicity up to 2,000mcg of GM-CSF dose; however, there was possible negative correlation between very high serum GM-CSF levels and PFS in patients with small liver metastasis. Therefore, our current standard care treatment uses 1,500 mcg of GM-CSF to avoid potential detrimental effects of high-dose GM-CSF.

The dosing of IPI+NIVO noted to be IPI 1mg/kg and 3mg/kg for the first four doses has been studied in a number of cancer types. It has been shown to be safe, and with less toxicity as evidenced in [NCT01454102].

Regarding the dosing of nivolumab, following the combination IPI+NIVO dosing for the first four doses the every 4-week schedule (Q4W) of NIVO will be more convenient for subjects. Based on pharmacokinetic modeling, the 480 mg Q4W (after steady state is reached with 3 mg/kg or 240 mg every 2 weeks) will provide steady-state average concentrations similar to 3 mg/kg or 240 mg Q2W, which has been shown to provide longer survival in NSCLC patients. However, 480 mg Q4W is expected to result in higher (approximately 20%) steady-state maximum concentration (peaks), and lower (approximately 10%) steady-state trough concentrations compared to steady state of 3 mg/kg Q2W. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose was identified. In addition, the exposure-response relationship for safety is flat. Thus, a slight increase in the steady-state maximum concentration is not expected to increase the safety risk of nivolumab. However, a marginal decrease in steady-state trough concentration is not expected to reduce the efficacy as high trough concentrations and > 90% intra-tumoral receptor occupancy are still maintained at 480 mg Q4W dose. Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profile to 3 mg/kg Q2W.

5.3 Procedure of Immunoembolization

5.3.1 Hospital Admission

Patients will be admitted to Thomas Jefferson University Hospital and undergo immunoembolization on Day #2, following IPI + NIVO on Day #1.

5.3.2 Access of the hepatic artery

An angiogram of the hepatic arteries will be obtained by the established technique. Non-ionized contrast will be used for angiographic studies to minimize the risk for allergic reactions. One of the hepatic lobes will then be treated based on the locations and sizes of the tumors. The proper arterial catheter placement, appropriate perfusion pattern to targeted tumors and existence of arteriovenous shunting that may cause pulmonary embolism by ethiodized oil will be thoroughly evaluated by angiography prior to the

embolization procedure. Such a degree of shunting is rarely ever seen in this patient population but discretion of the interventional radiologist will be used if shunting identified.

5.3.3 Embolization

For the patients who receive immunoembolization with GM-CSF, 3.5ml of Leukine® Liquid (1,500 mcg of GM-CSF) will be used. This solution will be emulsified in ethiodized oil (Ethiodol®) by repeated transfer of the two liquids between syringes connected via a stopcock. The amount of ethiodized oil administered is calculated based on tumor volume (1 ml per cm of summed tumor diameters). The actual amount of ethiodized oil will be decided based on the angiographic findings, including the degree of tumor vascularity and flow within the target hepatic artery. However, the maximum dose of ethiodized oil **will not** exceed 20 ml. The GM-CSF/ethiodized oil mixture will be done in the angiography suite immediately prior to the intraarterial delivery. When an emulsion has formed, the GM-CSF/ethiodized oil mixture will be slowly injected into the hepatic artery. Endpoints for the infusion of ethiodized oil will be delivery of the planned volume or the appearance of larger order portal vein branches. The perfusion pattern to the targeted tumors will be monitored during the injection of the ethiodized oil. Following this injection, gelatin sponge particles (1-2 mm size) will be infused into the hepatic artery until stasis of antegrade flow is obtained.

The immunoembolization procedure will be repeated every 3 weeks for the first 4 cycles and then if patient has shown evidence of tumor response, IEMBO may continue on maintenance every 4 weeks until disease progression or limiting toxicities. If the tumor is confined to a single lobe of the liver, embolization will be repeated to that lobe but interval between treatments may be extended up to every 6 weeks at the discretion of the treating physician. If the liver metastases are located in the both lobes of the liver, each hepatic lobe will be treated alternately. Variant arterial anatomy may require departure from this principle. Examples include a left lobe with dual supply from the left gastric artery and proper hepatic artery. The latter may be treated along with the right lobe.

5.4 Treatment Regimen Combination

Patients will be seen in the outpatient office on Day #1 of every cycle and receive administration of ipilimumab and nivolumab or once in maintenance phase nivolumab alone. On Day #2 they will undergo IEMBO consisting of intra hepatic artery administration of GM-CSF (1500mcg) mixed with ethiodized oil emulsion, followed by embolization of the hepatic artery with gelatin sponge particles under the care of interventional radiology. Patients will undergo this combination intervention every 3 weeks for 12 weeks unless significant disease progression, limiting toxicity, or withdrawal of consent. Interim imaging after 2 cycles will be peformed to ensure there has not been rapid progression. After four combination treatments if noted to have CR, PR, or SD patients will be offered maintenance therapy with combination intervention every 4 weeks until disease progression, limiting toxicity, or withdrawal of consent. When undergoing every 4 week maintenance patients will receive NIVO on Day #1 and IEMBO on Day #2 of each 28 day cycle.

5.5 Risks

There may be an increased risk of adverse events such as immune hepatitis or other liver toxicities with the combination therapy than would be seen with each treatment alone. See

section 6.2 for list of comprehensive adverse events and potential risks associated with the treatment.

5.6 Prior and Concomitant Therapy

For immune-related adverse events, steroid treatment will be allowed if it is tapered to 5 mg of prednisone or less before initiation of next cycle. Patients cannot have had prior exposure to anti-CTLA4 or anti-PD1 therapy. They cannot have had prior regional liver directed therapy but may have had liver resection or focal ablation. Palliative radiation is allowed during treatment. Patients who had cellular immunotherapy must have a washout period of at least 90 days prior to first treatment cycle. Patients who had other systemic therapies or radiation treatment must have a least a two week washout period prior to first treatment cycle. Bone strengthening agents such as zolendronic acid or denosumab are also allowed for bone metastases.

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule
See Appendix (Section 15.1)

6.1.1 Initial visit

A complete physical examination will be done within the four weeks prior to the initiation of the treatment. The tests and procedures described will be discussed with patients. The detailed treatment procedure and possible side effects will be discussed with patients and verbal and written consent for the treatment will be obtained. The tests and procedures listed below will be ordered after patients sign the consent form. If patients already have had tests performed as part of their standard care, the results of the tests will be recorded.

Once eligibility for the study is confirmed, the embolization procedure will be scheduled through Cardiovascular Interventional Radiology (CVIR).

The following studies and procedures must be performed within 4 weeks of initiation of treatment except pregnancy test (within 2 weeks). All abnormal and normal results must be recorded.

1. Medical history to include determination of tumor-related symptoms
2. Physical examination to include ECOG performance status, patient height and weight, vital signs.
3. Liver biopsy: Core biopsy of the liver tumor to confirm the diagnosis of metastatic uveal melanoma and to evaluate the host response to tumor. A separate standard procedure consent form must be obtained for biopsy of liver tumor.
4. Contrast-enhanced CT or MRI of the brain, CT of the chest (without contrast), CT of abdomen and pelvis (with and without contrast), and MRI of the abdomen (with and without contrast)
5. Blood tests to include the following:
   Complete blood count (CBC) with differential white blood cell count
   Serum laboratory studies including total bilirubin, SGOT (AST), SGPT (ALT), LDH, alkaline phosphatase, albumin, creatinine, BUN, glucose, calcium, phosphorus, CRP, PT, PTT, INR, TSH, T3, T4, ACTH and Cortisol
6. Pregnancy test (only in women of childbearing potential). The test must be done within 2 weeks prior to initiation of treatment.

6.1.2 Evaluation during treatment

An interim history and physical examination will be performed prior to each subsequent treatment cycle to assess toxicities and disease status. This is to be done upon admission to the hospital and at outpatient appointments for immunotherapy infusion.

CBC with differential, platelet count, liver function tests and renal function tests and LDH will be done prior to the treatment, day of IEMBO, day after IEMBO and, and then weekly unless more frequently is required. In the event that a subject is no longer receiving infusion on Day 1 (IPI and/or NIVO), and only receiving IEMBO – Day 1 labs (CRP, TSH, & T4) will be drawn prior to IEMBO on Day 2.

Due to possibility of abrupt onset endocrinopathy TSH,ACTH, T3, T4, cortisol will also be ordered as part of monitoring for side effects related to IPI+NIVO and NIVO the week prior to scheduled infusion. On Day 1 of each cycle TSH and T4 will also be ordered.. Lipase will be ordered on as needed basis.

Coagulation tests (PT, PTT, INR) will be done prior to each embolization.

Sixty (60) ml of blood will be drawn for immunological testing prior to each cycle beginning. Additionally, 10 ml of blood will be drawn before, 1 hours and on Day 3 after the individual IEMBO for cytokine measurements. Also up to an additional 10ml of blood will be drawn prior to the initial cycle for purposes of determining tumor mutational load. Study blood will be collected for the first 6 cycles of treatment, then at 12 and 24 months and at End of Treatment visit, even if visit is before the completion of 6th cycle.

Eligibility criteria will be applied to each treatment. Only the patients who fulfill the eligibility criteria will be offered further embolization treatment. If follow-up test results indicate that patients have become ineligible for treatment, the next treatment will be postponed for a maximum of 4 weeks. If sufficient improvement is not seen during this period to restore eligibility for the next treatment, they will be removed from the study.

6.1.3 Post-embolization liver biopsy

Three weeks after the first embolization and prior to the second embolization, the second liver biopsy will be performed to evaluate the host response to tumor *if technically feasible.* A separate standard procedure consent form must be obtained for biopsy of the liver tumor.

6.1.4 Office visit after 4 cycles

After the fourth cycle patients will be evaluated for response. The tests and procedures described below will be performed.

1. Medical history to include determination of tumor-related symptoms
2. Physical examination to include ECOG performance status, patient height and weight, vital signs
3. CT of the chest (with contrast), CT of abdomen and pelvis (with and without contrast), and MRI of the abdomen (with and without contrast)
4. Blood tests to include the following

Complete blood count (CBC) with differential white blood count. Serum laboratory studies including total bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, albumin, TSH, creatinine, BUN, glucose, calcium, and phosphorus. Sixty (60) ml of blood will also be drawn for immunological testing.

After the completion of 4 treatments, continuation of the treatment will be offered to patients who have demonstrated clinical benefit from the treatment and have not experienced any CTC grade 4 toxicity while participating in this study. If the patient started with unilobar disease but develops liver metastases in the contralateral lobe treatment to the contralateral lobe with immunoembolization and continuation of the treatment will be allowed.

If patients have progression of liver metastases, or progression of extra-hepatic metastases that require a change in systemic therapy (palliative radiation or surgery allowed as per discretion of investigator) determined by RECIST 1.1, or experienced serious side effects, patients will be removed from the study and appropriate medical advice regarding alterative treatment options will be provided (See Section 6.1.6 Completion of the study).

If patients have unequivocal progression of hepatic metastasis prior to the visit after 4 treatments, they may be removed from the study at the discretion of the investigators and appropriate medical advice will be provided. In that case, patients will be followed every 3 months to document their medical condition until their death. Follow-up over the telephone will be performed for patients unable to return for examination. If there is a mixed response seen at the interim scan completed between cycles 2 and 3, and it is deemed patient is getting clinical benefit, they will be allowed to continue with study treatment.

If patients have stabilization of hepatic metastasis but progression of extra-hepatic metastasis after 4 treatments, two additional IEMBO treatments, 4 weeks apart, will be allowed as long as hepatic metastasis is stable. This would prevent the early removal of patients with pseudo-progression of extra-hepatic metastasis. If follow-up imaging studies show further progression of extra-hepatic metastasis after 2 additional IEMBO + NIVO treatments, patients will be removed from the study. In that case, patients will be followed every 3 months to document their medical condition until their death. Follow-up over the telephone will be performed for patients unable to return for examination.

After the completion of first four treatment cycles, if disease stabilization is determined (at 12 weeks), continuation of treatment on maintenance phase may be offered as a combination of IEMBO +NIVO or, in the event of NIVO-related toxicity, IEMBO alone.

6.1.5 Additional outpatient visits prior to infusion of IPI+NIVO or NIVO alone.
Patients will be seen in the outpatient setting prior to each infusion of IPI+NIVO or NIVO alone during maintenance.

During maintenance phase, after the completion of every two treatments patients will be seen by both medical oncology and interventional radiology for evaluation. A complete physical examination will be done by a study physician.

CT scan of the chest (with contrast), CT of abdomen and pelvis (with and without contrast) and MRI of the abdomen (with and without contrast) will be obtained prior to the subsequent follow-up office visits after every two treatments (NIVO + IEMBO).

The decision to continue treatment will be based on the results of the imaging and laboratory tests and the physical status of the patients. Unless patients become ineligible based on the inclusion/exclusion criteria, or unless patients develop rapid progression, or unless patients experience an unacceptable serious adverse event, the combination treatment will be continued.

Patients who experience progressive disease by RECIST criteria without clinical deterioration may continue on protocol therapy until their next scheduled scan if the investigator feels the patient may be having clinical benefit and may experience a delayed or atypical response. Only patients who have no progression of symptoms of cancer, no decline in performance status, and no progression of tumor at a critical anatomic site (e.g., cord compression) will be eligible for the treatment beyond progression. If the next scheduled scan shows a further increase in tumor measurements (>10% RECIST target lesions or unequivocal progression of non-target lesions) from the scan that first suggested progression, patient will be deemed to have true progression and patient will be removed from study. It the next scheduled scan does not show further progression, patient will remain on study treatment.

For patients who achieved PR, CR, or SD in the liver metastases after embolization, tumor measurements should be continued after every 2 IEMBO treatments for up to 2 years after initiation of protocol therapy or until PD is confirmed.

6.1.6 Completion of the study

Patients will receive study treatment for a maximum of two years or until disease progression. The study will be completed if progression of liver metastases is confirmed by the follow-up imaging studies. Patients will also be removed if they develop progression of extra-hepatic metastases for two consecutive imaging studies unless palliative radiation or surgical resection of progressive disease is feasible. Patients will be removed if they develop an unacceptable serious adverse event. If they fail to fulfill the eligibility criteria for the combination treatment, the patient will also be removed from the study.

At the time of study completion, the following studies and procedures will be performed:

1. Medical history to include determination of tumor-related symptoms
2. Physical examination to include ECOG performance status, weight, and vital signs
3. CT of the chest (with contrast), CT of abdomen and pelvis (with and without contrast), and MRI of the abdomen (with and without contrast)…*if they are not ordered within 4 weeks of completion of the study*
4. Blood draw for tests to include the following:
   Routine: complete blood count (CBC) with differential white blood count, serum laboratory studies including total bilirubin, SGOT, SGPT, LDH, alkaline phosphatase, albumin, TSH, creatinine, BUN, glucose, calcium, and phosphorus;
   Research: biomarker testing (60 ml) and immunological testing (10 ml).

6.1.7 Follow-up after study completion

All patients, including patients who discontinue protocol therapy because of toxicity or progressive disease must be followed every three months up to a minimum of 1 year to determine clinical status and to document time to progression and duration of survival. Telephone contact is allowed for this purpose.

6.2 Adverse Events and Potential Risks

Please see appendix 16.2 detailing potential adverse drug events (ADRs) that may be attributable to ipilimumab and nivolumab combination or nivolumab alone. In general side effects related to ipilimumab and nivolumab are considered immune related adverse events and include but are not limited to dermatitis, hepatitis, pneumonitis, colitis, endocrinopathy (including hypophysitis and thyroiditis), and nephritis. Appendix tables adopted from Investigator Brochure addendum.

6.3 Dose Delays and Dose Modifications

6.3.1 Attributed to Immunoembolization with GM-CSF
If CTC Grade 4 systemic and or local toxicities related to GM-CSF are observed, no further dose will be offered, with the exception of Grade 4 AST/ALT elevation as long as resolves within 7 days.

6.3.2 Attributed to Ipilimumab, Ipilimumab or Nivolumab, or Nivolumab alone.
See Appendix 3 for management of immune related toxicities.

6.3.3 Attributed to combination of Ipilimumab and Nivolumab and Immunoembolization or Nivolumab and Immunoembolization
Combination treatment could be postponed for up to 10 weeks (from the date of next scheduled treatment). if patients need a treatment break for immune related toxicity. During combination treatment with IPI and NIVO, depending on type and severity of toxicity, patient may be able move onto the maintenance phase of NIVO + IEMBO and drop the IPI before the full four combination doses are given. Likewise, NIVO may also be dropped and patient may be able to continue on with IEMBO only, if the investigator feels patient is receiving clinical benefit from it. These determinations may be made at the investigator's discretion, in consideration of patient safety.

A window of +/- 3 days is permitted between each treatment cycle beginning at cycle 2 and will not be characterized as dose or treatment delay.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

The trial will enroll 13 patients in the first stage. If there are 8 or fewer responses in these 13 patients, the study will be stopped. If the trial goes on to the second stage, 22 additional patients will be accrued for a total of 35 patients. The sample sizes for each stage are computed for optimal minimax design to test the null hypothesis that hepatic metastasis stabilization rate ≤ 60% versus the alternative that stabilization rate > 80% using one-sided test with a target a type I error rate of 0.05.

7.2 Statistical Methods

The trial is designed with the potential for early termination in the case of a poor hepatic metastasis stabilization rate (hepatic response). The design will be a two-stage optimal minimax design using the method of Simon, augmented with admissible choices. Choice of design is guided by a desire to stop the trial early if the actual metastasis stabilization rate is 60% (as experienced with IEMBO alone) or less. If the metastasis stabilization rate is 80% or greater, we would like to have a low probability of failing to conclude that IEMBO + IPI + NIVO is effective. The trial will enroll 13 patients in the first stage. If in these 13 patients, 8 or fewer patients have hepatic metastasis stabilizations, the study will be stopped. If the trial goes on to the second stage, 22 additional patients will be accrued for a total of 35 patients. The combination IEMBO + IPI + NIVO will be considered ineffective if there are 25 or fewer responses (hepatic metastasis stabilizations) in 35 patients. With this design, we have no more than a 19% chance of concluding that combination IEMBO + IPI + NIVO is ineffective ($\leq$60% success rate) when the success rate is at least 80%. Similarly, we have no more than a 5% chance of concluding effective ($\geq$60% success rate) when it is ineffective. If the actual metastasis stabilizations rate is 60% or worse, we have at least a 0.65 probability that the trial will stop after the first 13 subjects.

7.2.1 Analysis Population

The evaluable population includes all subjects enrolled who receive at least four combination treatments (IPI + NIVO + IEMBO at initial every 3 week intervals or NIVO + IEMBO if IPI dropped due to toxicity and IEMBO alone if NIVO dropped due to toxicity) and complete assessment after four treatments.

The As-treated population includes all subjects who receive any treatment and will be used to evaluate baseline characteristics as well as all secondary endpoints for safety and efficacy as the collected data allows.

7.2.2 Primary Endpoint:

The primary endpoint is the best hepatic response (CR + PR + SD) by response criteria (RECIST 1.1) after four combination treatments. The estimate of the hepatic metastasis stabilization rate will be presented with corresponding 95% confidence intervals. The method of Atkinson and Brown will be used to adjust for the two-stage design.

7.2.3 Secondary and Exploratory (Correlative) Endpoints

1. All toxicities using the NCI CTCAE Version4.0.
2. PFS (hepatic and systemic PFS)
3. Overall survival
4. Systemic and local immune/inflammatory response correlatives
    a. Degree and classification of tumor-infiltrating cells
    b. Presence and changes in PD-L1 expression in tumor and tumor-infiltrating cells
    c. Changes in immune tumor microenvironment (immune gene signature)
    d. Tumor mutational burden prior to treatment
    e. Changes in TCR repertoire analysis (ImmunoSeq)
    f. Changes in cytokine levels (multiplex cytokine measurements)
    g. Changes in PBMC cell populations, including T cells and MDS.

The PFS and OS will be estimated using the Kaplan-Meier method. The toxicity rates will be estimated with corresponding 95% confidence intervals. Correlative endpoints including repeated measures of cytokine and molecular marker levels in tissue or serum will be analyzed using appropriate linear mixed effects models.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

8.1.1 *Adverse Event*

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

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 *Serious Adverse Event*

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

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

Adverse events are classified as serious or non-serious.

A ***serious adverse event*** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 *Adverse Event Reporting Period*

The adverse event reporting period for this trial begins when the patient receives the first treatment and ends 3 months after completion or withdrawl from the study. All adverse events that occur in trial subjects during the adverse event reporting period specified in the protocol will be reported, whether or not the even is considered treatment related.

The PI will follow adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.1.4 *Preexisting Condition*

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1.5 *General Physical Examination Findings*

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.1.6 *Post-study Adverse Event*

All unresolved adverse events should be followed by the investigator until the events are resolved to grade 1 or less, or become chronic, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should

become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.1.7 *Abnormal Laboratory Values*

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- Grade 3 or 4 lab abnormality other than what is otherwise explained elsewhere in the protocol
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

8.1.8 *Hospitalization, Prolonged Hospitalization or Surgery*

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified.

- *Relationship to Study Intervention*

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

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

1. Related (Possible, Probable, Definite)

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

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

c. The event abates when the intervention is discontinued.

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

2. Not Related (Unlikely, Not Related)

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

b. An alternate etiology has been established.

- *Expectedness*

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

- *Severity of Event*

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

- *Intervention*

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

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

The clinical course of each event should be followed until resolution to grade 1 or less, stabilization, becoming chronic, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

See form in appendix OHR-10 for recording of these events.

8.3 Reporting of Adverse Events

Any adverse events that is associated with study treatment and that is both serious and unexpected will be reported to the FDA by telephone, email, or fax within 7 days. All of the

investigators and the Thomas Jefferson University IRB will be notified as well. A follow-up safety report will be submitted within 15 days of initial notification.

In addition, Bristol-Myers Squibb will be notified within 24 hours of becoming aware of any serious adverse event.

8.4 Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the safety profile of this treatment and require close monitoring and rapid identification as there is specific guidelines for management of these toxicities. Notably, immune related adverse events, including Grade 4 hepatitis. Please see list of side effects and Immune-Related Adverse Event Guidance section and appendix 3 to further classify these events and subsequent management.

8.5 Data and Safety Monitoring Plan

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

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the Sidney Kimmel Cancer Center at Jefferson (SKCC) data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

Study site will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance(Worldwide.Safety@bms.com).

BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to *aepbusinessprocess@bms.com*.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

8.5.2 Data and Safety Monitoring Committee

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at) Thomas Jefferson University. The

Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. ***Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.*** A summary of the reporting requirements for KCC investigator initiated Phase I and Phase II studies are presented below.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

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

**NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

8.6 Unanticipated Problems

All incidents or events that meet criteria for unanticipated problems (UAPs) require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 10 working days of the investigator becoming aware of the event.

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

8.7 Adverse Events

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

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

8.8 Serious Adverse Events

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

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

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

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

9.0 EVALUATION OF RESPONSE

9.1 Evaluation of Clinical Response

Patients who receive at least one IEMBO treatment will be evaluable for clinical response, including survival. Patients who were not treated with IEMBO due to technical problems will not be included for evaluation of clinical response. Patients will first be evaluated with scans between Cycles 2 and 3 to insure no evidence of rapid progression. Initial radiographic response will be determined following four IEMBO treatments if both. Patients with SD, PR, or CR at this time will have repeat scans after every two treatment cycles.

9.2 Definition of Measurable Disease

Measurable disease

Measurable disease is defined by the presence of at least one measurable lesion as defined below and adapted from the RECIST 1.1 criteria (Eur J Cancer. 2009 Jan;45(2):228-47). All measurements must be recorded in metric notation. If measurable disease is restricted to a solitary lesion, its malignant nature should previously have been confirmed by cytology/histology.

Since some melanoma metastases contain melanin pigment and since successfully treated liver metastases tend to retain infused ethiodized oil, evaluation of radiological response after embolization treatments is generally difficult. Therefore, we will obtain both CT scan and MRI of the liver for the precise evaluation of radiological responses. However, the same modality will be used for measurement of the liver metastases and assessment of the response.

The longest diameter (LD) of the largest liver lesion should be ≥ 10 mm by CT scan or MRI in order to become eligible for the study.

Non-measurable disease

All other lesions including small lesions (<10 mm on CT scans) are considered "non-measurable". The following lesions are also considered as "non-measurable": Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, abdominal masses that are not confirmed and followed by imaging techniques, tumors treated by irradiation or by intra-tumor injection therapy.

9.3 Baseline Documentation of "Target" and "Non-Target" Lesions

Target Lesions (Indicator Lesions)

The target lesions are defined as measurable lesions that will be used for evaluation of response. For this protocol, target lesions require serial measurement of a longest diameter (LD) and should be ≥10 mm by CT scan or MRI at the time of study entry.

Target lesions (up to a maximum number of 6 for the liver metastases) must be identified and measured at baseline prior to the initiation of embolization. Target lesions must be selected on the basis of their size (LD) and suitability for repetitive measurements.

Non-Target Lesions

All other lesions (or sites of melanoma) must be identified as "non-target" and their location and characteristics must be recorded at baseline. During follow-up evaluations, these lesions must be followed as "present" or "absent".

9.4 Evaluation of overall response in the liver metastases

Clinical response in the liver metastases will be evaluated using CT scans or MRI of the abdomen initially following four combination treatments and then after every two IEMBO treatments. The same modality must be used for serial measurements of target lesions. The sum of the longest diameter (LD) of up to 6 target liver lesions will be used to determine response. The investigators must identify target indicator lesions and measure them prior to the first embolization as baseline. The investigators will then measure the same target lesions after every two IEMBO treatments.

The sum of the baseline LDs will be compared to the sum of LDs after every two IEMBO treatments following the scans after the first four treatments. New lesions will be defined as lesions that appear in the treated lobe(s) of the liver after the last evaluation and should be ≥ 10 mm in longest diameter. Development of new lesion(s) in an untreated lobe (area) of the liver **will not** be considered as "Progressive Disease" for evaluation of liver response. These lesions will be treated in the subsequent embolization procedures and

they will be included in the evaluation for response after completion of two additional embolizations.

Target Liver Lesions	Non-Target Liver Lesions	New Liver Lesions in the treated lobes	Overall Liver Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by the follow-up assessment using the same imaging test at a minimum interval of 4 weeks. The patients who have a CR or PR without confirmatory assessment will be categorized as SD. In the case of SD, follow-up measurements must have met the SD criteria at least once at a minimum interval of 4 weeks. The patients who have a SD without confirmatory assessment will be categorized as PD.

9.5 Response criteria for liver metastases

The response of liver metastases will be evaluated by MRI or CT scans using the criteria

Complete Response (CR)	Disappearance of all target and non-target liver lesions
Partial Response (PR)	$\geq$ 30% decrease in the sum of the longest diameters ("sum LD") relative to baseline sum LD with at least stable non-target liver lesions
Stable Disease (SD)	Absence of change which would qualify as response or progression
Progression (PD)	$\geq$ 20% increase in the sum LD in target liver lesions or unequivocal progression of non-target liver lesions in the treated lobe(s) Appearance of one or more new liver lesions $\geq$10 mm in the treated lobe(s)

adapted from the international criteria proposed by RECIST 1.1. However, since there can be post embolization changes in liver tumors that can sometimes be read as lesion enlargement, post treatment changes will be considered when lesions are measured.

9.6 Progression Free Survival

Progression Free Survival (PFS) is measured from the start of the treatment to confirmation of progression of disease by either imaging tests or physical examination. Date and sites of progression will be recorded. Progression free interval for hepatic metastases and progression free interval for extra-hepatic metastasis will be measured in aggregate and separately.

9.7 Overall survival

Overall survival (OS) is measured from the start of the treatment to death of patients. Date and cause of death will be recorded. The cause of death will be categorized as either cancer-related or cancer-unrelated.

10.0 CORRELATIVE STUDIES

10.1 Collecting Samples

Peripheral blood samples will be collected prior to and following combination treatments as outlined in the study calendar.

10.2 Biopsies

Patients will need to have biopsy or access to archival tissue prior to treatment. Three weeks after the first embolization and prior to the second embolization, the second liver biopsy will be performed to evaluate the host response to tumor *if patients consent and technically feasible.* A separate standard consent form must be obtained for biopsy of the liver tumor. Biopsy at time of progression is also options *if patients consent and technically feasible.*

10.3 Evaluations

Systemic and local immune/inflammatory response correlatives

Local Immune Responses:

a. Degree and classification of tumor-infiltrating cells
b. Presence and changes in PD-L1 expression in tumor and tumor-infiltrating cells
c. Changes in immune tumor microenvironment (immune gene signature)

Systemic immune responses:

d. Changes in leukocyte subpopulations in the peripheral blood, including activated T cells as well as MDSC
e. Changes of serum cytokine levels before and after treatment to include IL-6, IL-8, TNF-alpha, IFN-gamma, and GM-CSF by multiplex cytokine assays.
f. Changes in TCR repertoire analysis (ImmunoSeq)

Tumor mutational load will also be assessed on the primary liver tumor biopsy prior to treatment and corresponding blood sample will be obtained to provide as control for possible characterization of germline mutations.

Any residual blood or tissue samples may be subjected to additional testing where appropriate.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

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

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

11.2 Source Documents

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

11.3 Data Collection

The Redcap database utilized for this study will be the primary data collection instrument for the study. All data requested in Redcap must be recorded. All missing data must be explained.

11.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

12.0 STUDY MONITORING, AUDITING, AND INSPECTING

12.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

KCC Investigator Initiated Phase II Studies
Phase II studies require continuous monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRMO and the DSMC. Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial at each new dose level, prior to dose escalation.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other personal health information (PHI) is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI. If for any reason the PI of the trial disagrees with the conclusions of the Medical Monitor or DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution.

The summary of all discussions of adverse events are included in the KCC investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRBs may, based on the monitor's recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

12.2 Auditing and Inspecting

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

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

12.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where

significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

13.0 ETHICAL CONSIDERATIONS

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

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

13.2 Subject Stipends or Payments

There is no compensation for participation in this study.

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15.0 APPENDICES

15.1 Study Schedule

Events	Screening Evaluation	Pretreat assessment	Initial IPI+NIVO	IEMBO			After 4 cycles	Subsequent NIVO	Subsequent IEMBO	Follow up Visits	Exit
TIME	Within 4 weeks prior to enrollment	Within 4 weeks prior to treatment	Day 1 of each 21 day cycle for first four	Day 2 of each 21 day cycle for first four	Day 3 of each 21 and 28 day cycle	Weekly while getting IEMBO	Appt. after first 4 cycles	Day 1 of each 28 day cycle after first four (*9)	Day 2 of each 28 day cycle after first four	Every 8 week outpatient appt after 12 weeks	Exit
Informed Consent	X										
Demographics	X										
Medical History	X	X (*4)	X	X			X	X	X	X	X
Physical Exam	X	X (*4)	X	X			X	X	X	X	X
Performance Status	X	X (*4)	X				X	X	X	X	X
Concomittent Medications	X	X (*4)	X				X	X	X	X	X
CBC with Diff	X	X (*4)	X(*5)	X	X	X	X	X(*5)	X		X
PT, INR, PTT	X			X					X		
Serum Chemistry (*1)	X	X (*4)	X(*5)	X	X	X	X	X(*5)	X		X
TSH		X (*4)	X(*5)			X(*7)	X	X(*5, 7, 10)			
LDH	X	X (*4)	X(*5)	X	X	X	X	X(*5)	X		X
CRP		X	X (10)		X		X	X(10)			
Pregnancy Test (*2)	X	X (*2)									
Study Blood			X (*3, 10, 11)	X(*3)	X		X	X(*3, 5, 10, 11)	X(*3)		X(*11)
Liver Tumor Bx		X (*6)		X(*6)							
CT C/A/P	X	X (*4)					X			X	X(*8)
MRI Abdomen	X	X (*4)					X			X	X(*8)
CT or MRI Brain	x	X (*4)									
Tumor Measurement		X					X			X	X(*8)
IPI+NIVO			X								
NIVO								X			
IEMBO				X					X		
Toxicities and AEs		X (*4)	X	X	X		X	X	X	X	X

*1: Comprehensive metabolic panel including total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, albumin, creatinine, BUN, glucose, calcium, phosphate.

*2: For females of childbearing potential and within 2 weeks of start of treatment, and on Day 1 of every cycle or (Day 2 if only receiving Iembo.).

*3: 60 ml blood for immunologic testing prior to each cycle, 10 ml drawn before, 1 hour and at Day 3 after IEMBO for cytokines There is a 15 minute window for initial blood draw as patients are sometimes mid-transport at one hour post IEMBO.

*4: Tests can be skipped if screening evaluation is performed within 4 weeks prior to scheduled treatment.

*5: May be done within 3 days prior for Day 1 visit.

*6: Biopsy or access to Archival tissue needed prior to treatment. Biopsy Day 2 of Cycle 2 before second Immunoembolization but may be performed one week before Cycle 2

*7: Endrocrine labs will be checked one week prior to each infusion and at the next infusion.

*8: If not completed within 4 weeks of Exit.

*9: There is a window of 3 days +/- permitted between each treatment cycle, beginning at Cycle 2.

*10 In the event pt. is no longer receiving infusion on Day 1, 60 ml study blood and CRP can be drawn on Day 2 prior to IE.

* 11 Study blood will be taken at the first 6 cycles of treatment, then yearly, and at Exit/EOT.

15.2 Adverse Events and Potential Risks

The following tables and text are adopted from Investigator Brochure Addendum No. 1 28-Sep-2016 Addendum No. 1 to Investigator Brochure Version 15, dated 24-Jun-2016, for BMS-936558 (Nivolumab).

Adverse Drug Reactions from Clinical Studies

Any adverse drug reactions (ADRs) included in this section were identified by the Sponsor based on the nature and frequency of observed events (from both open-label and blinded clinical studies) and reasonable evidence of causal association with nivolumab. The ADRs as described in this section are considered to be expected. For example, if an ADR is described as serious (indicated by "Y") in the table below but not life threatening or fatal (indicated by "n"), then the Sponsor would not consider a life-threatening or fatal occurrence to be expected. Similarly, if ADRs are described as non-serious, then serious, life threatening, and/or fatal occurrences would not be considered expected. Additionally, if an ADR is described as fatal then a less severe outcome of life threatening is expected.

The ADRs for nivolumab are listed by System Organ Class in Table 16.2-1 and Table 16.2-2. The overall frequency of the ADR represents the frequency for all ADRs regardless of seriousness. The sponsor has included information in the table as to the nature of the ADR, including serious, life threatening or fatal outcomes. For all events in the table, non-serious events are expected.

Frequency categories are defined using the following convention: very common ≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Cardiac Disorder	Tachycardia	Uncommon 17 (0.18)	n	n	n
	Atrial fibrillation[a]	Rare 6 (0.07)	**Y** 2 (0.02)	n	n
	Arrhythmia	Rare	*n*	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		2 (0.02)			
	Ventricular arrhythmia	Rare 1 (0.01)	**Y** 1 (0.01)	n	n
Ear and Labyrinth Disorders	Vertigo	Uncommon 22 (0.24)	n	n	n
Endocrine Disorders	Hypothyroidism	Common 440 (4.78)	**Y** 14 (0.14)	n	n
	Hyperthyroidism	Common 141 (1.53)	**Y** 5 (0.05)	n	n
	Hyperglycaemia	Uncommon 72 (0.78)	**Y** 16 (0.17)	**Y** 1 (0.01)	n
	Adrenal Insufficiency	Uncommon 52 (0.56)	**Y** 28 (0.31)	**Y** 1 (0.01)	n
	Hypophysitis	Uncommon 32 (0.35)	**Y** 16 (0.17)	n	n
	Thyroiditis	Uncommon 25 (0.27)	n	n	n
	Diabetes mellitus	Uncommon 19 (0.21)	**Y** 4 (0.04)	n	n
	Hypopituitarism	Uncommon 16 (0.17)	**Y** 5 (0.05)	n	n
	Autoimmune thyroiditis	Uncommon 11 (0.12)	**Y** 1 (0.01)	n	n
	Autoimmune hypothyroidism	Rare 3 (0.03)	n	n	n
	Diabetic ketoacidosis	Rare 3 (0.03)	**Y** 3 (0.03)	**Y** 1 (0.01)	n
Eye Disorders	Dry eye[a]	Uncommon 42 (0.46)	n	n	n
	Vision blurred	Uncommon 32 (0.35)	n	n	n
	Uveitis	Uncommon 12 (0.13)	**Y** 2 (0.02)	n	n
	Iridocyclitis	Rare	**Y**	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		3 (0.03)	1 (0.01)		
Gastrointestinal Disorders	Diarrhea	Common 783 (8.50)	**Y** 68 (0.74)	n	n
	Nausea	Common 700 (7.60)	**Y** 23 (0.25)	n	n
	Vomiting	Common 289 (3.14)	**Y** 26 (0.28)	n	n
	Constipation	Common 223 (2.42)	n	n	n
	Abdominal Pain	Common 222 (2.41)	**Y** 13 (0.14)	n	n
	Dry mouth	Common 157 (1.70)	n	n	n
	Colitis	Common 98 (1.06)	**Y** 70 (0.78)	n	**Y** 2 (0.02)
	Stomatitis	Uncommon 86 (0.93)	**Y** 4 (0.04)	n	n
	Mucosal inflammation	Uncommon 68 (0.74)	**Y** 4 (0.04)	n	n
	Gastritis[a]	Uncommon 16 (0.17)	**Y** 4 (0.04)	n	n
	Pancreatitis	Uncommon 15 (0.16)	**Y** 7 (0.08)	n	n
	Autoimmune colitis	Rare 5 (0.05)	**Y** 2 (0.02)	n	n
	Mouth ulceration[b]	Rare 4 (0.04)	**Y** 1 (0.01)	n	n
	Pancreatitis acute	Rare 4 (0.04)	**Y** 3 (0.03)	n	n
	Mucosal	Rare 1 (0.01)	n	n	n
General disorders and administration site conditions	ulceration	Very Common 1390 (15.09)	**Y** 28 (0.30)	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Pyrexia	Common 326 (3.54)	**Y** 41 (0.45)	n	n
	Asthenia	Common 311 (3.38)	**Y** 2 (0.02)	n	n
	Chills[a]	Common 146 (1.58)	**Y** 4 (0.04)	n	n
	Oedema peripheral	Common 120 (1.30)	**Y** 3 (0.03)	n	n
	Oedema	Uncommon 16 (0.17)	n	n	n
	Face oedema	Uncommon 14 (0.15)	n	n	n
	Localised oedema	Uncommon 9 (0.10)	**Y** 1 (0.01)	n	n
	Peripheral swelling	Uncommon 9 (0.10)	n	n	n
	Generalised oedema	Rare 5 (0.05)	n	n	n
	Periorbital oedema	Rare 4 (0.04)	n	n	n
	Swelling face	Rare 4 (0.04)	**Y** 1 (0.01)	n	n
Hepatobilliary Disorders	Autoimmune hepatitis	Uncommon 18 (0.20)	**Y** 14 (0.15)	**Y**[b] 1 (0.01)	n
	Hepatitis	Uncommon 11 (0.12)	**Y** 8 (0.09)	n	n
	Hepatitis acute	Rare 3 (0.03)	**Y** 3 (0.03)	n	n
Immune System Disorders	Infusion related reaction	Common 152 (1.65)	**Y** 21 (0.23)	**Y** 1 (0.01)	n
	Hypersensitivity	Uncommon 70 (0.76)	**Y** 9 (0.10)	**Y** 1 (0.01)	n
	Anaphylactic reaction	Rare	**Y**	**Y**	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		4 (0.04)	3 (0.03)	2 (0.02)	
	Sarcoidosis[a]	Rare 4 (0.04)	**Y** 2 (0.02)		
Infections and Infestations	Upper respiratory tract infection	Uncommon 31 (0.34)	n	n	n
	Bronchitis	Uncommon 10 (0.11)	n	n	n
Investigations	Aspartate aminotransferase increased	Common 257 (2.79)	**Y** 23 (0.25)	n	n
	Alanine aminotransferase increased	Common 239 (2.59)	**Y** 27 (0.329)	n	n
	Lipase increased	Common 163 (1.77)	**Y** 13 (0.14)	n	n
	Blood alkaline phosphatase increased[a]	Common 127 (1.38)	**Y** 6 (0.07)	n	n
	Amylase increased	Common 102 (1.11)	**Y** 4 (0.04)	n	n
	Blood creatinine increased[a,]	Common 100 (1.09)	**Y** 3 (0.03)	n	n
	Blood thyroid stimulating hormone increased[a]	Common 92 (1.00)	n	n	n
	Blood bilirubin increased	Uncommon 49 (0.53)	**Y** 4 (0.04)	n	n
Metabolism and Nutrition Disorders	Decreased appetite	Common 536 (5.82)	**Y** 5 (0.05**)**	n	n
	Hyponatraemia	Uncommon 87 (0.94)	**Y** 17 (0.18)	n	n
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Common 358 (3.89)	**Y** 3 (0.03)	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Myalgia	Common 202 (2.19)	**Y** 2 (0.02)	n	n
	Pain in extremity	Uncommon 74 (0.80)	n	n	n
	Back pain	Uncommon 64 (0.69)	**Y** 2 (0.02)	n	n
	Musculoskeletal pain	Uncommon 50 (0.54)	n	n	n
	Arthritis	Uncommon 26 (0.28)	**Y** 3 (0.03)	n	n
	Musculoskeletal chest pain	Uncommon 13 (0.14)	n	n	n
	Polyarthritis	Uncommon 13 (0.14)	**Y** 4 (0.04)	n	n
	Bone pain	Uncommon 11 (0.12)	n	n	n
	Neck pain	Rare 8 (0.09)	n	n	n
	Polymyalgia rheumatica[b]	Rare 6 (0.07)	**Y** 1 (0.01)	n	n
	Myositis[a]	Rare 5 (0.05)	**Y** 3 (0.03)	n	n
	Musculoskeletal discomfort	Rare 3 (0.03)	n	n	n
	Osteoarthritis	Rare 3 (0.03)	n	n	n
	Pain in jaw	Rare 2 (0.02)	n	n	n
	Polymyositis[a]	Rare 1 (0.01)	**Y** 1 (0.01)	n	**Y** 1 (0.01)
	Rhabdomyolysis[a]	Rare 1 (0.01)	**Y** 1 (0.01)		
Nervous System Disorders	Headache	Common 215 (2.33)	**Y** 4 (0.04)	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Dizziness	Uncommon 83 (0.90)	**Y** 3 (0.03)	n	n
	Neuropathy peripheral	Uncommon 59 (0.64)	**Y** 4 (0.04)	n	n
	Peripheral sensory neuropathy	Uncommon 24 (0.26)	**Y** 1 (0.01)	n	n
	Cranial nerve disorder[a]	Uncommon 12 (0.13)	**Y** 6 (0.07)	n	n
	Peripheral motor neuropathy	Rare 7 (0.08)	**Y** 2 (0.02)	n	n
	Polyneuropathy	Rare 7 (0.08)	**Y** 2 (0.02)	n	n
	Burning sensation	Rare 5 (0.05)	n	n	n
	Encephalitis	Rare 2 (0.02)	**Y** 2 (0.02)	n	**Y**[b] 1 (0.10)
	Guillain-Barre syndrome	Rare 2 (0.02)	**Y** 2 (0.02)	n	n
	Myasthenia gravis	Rare 2 (0.02)	**Y** 2 (0.02)	n	n
	Demyelinating polyneuropathy[b]	Rare 1 (0.01)	**Y** 1 (0.01)	n	n
	Demyelination[b]	Rare 1 (0.01)	**Y** 1 (0.01)	n	n
	Myasthenic syndrome	Rare 1 (0.01)	**Y** 1 (0.01)	n	n
Renal and Urinary Disorders	Acute kidney injury	Uncommon 26 (0.28)	**Y** 20 (0.22)	**Y** 2 (0.02)	n
	Renal failure	Uncommon 15 (0.16)	**Y** 4 (0.04)	n	n
	Tubulointerstitial nephritis	Uncommon 9 (0.10)	**Y** 8 (0.09)	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Autoimmune nephritis	Rare 4 (0.04)	**Y** 3 (0.03)	n	n
	Nephritis	Rare 1 (0.01)	n	n	n
Respiratory, Thoracic, and Mediastinal Disorders	Pneumonitis	Common 247 (2.68)	**Y** 133 (1.44)	**Y** 7 (0.08)	**Y** 9 (0.10)
	Dyspnoea	Common 231 (2.51)	**Y** 35 (0.38)	**Y** 1 (0.01)	**Y** 3 (0.03)
	Cough	Common 222 (2.41)	**Y** 3 (0.03)	n	n
	Interstitial lung disease	Uncommon 27 (0.29)	**Y** 18 (0.20)	**Y**[b] 1 (0.01)	n
	Respiratory failure[a]	Uncommon 17 (0.18)	**Y** 15 (0.16)	**Y** 2 (0.02)	**Y** 6 (0.07)
	Lung infiltration	Rare 7 (0.08)	**Y** 2 (0.02)	n	n
	Organising pneumonia	Rare 2 (0.02)	**Y** 2 (0.02)	n	n
	Respiratory distress syndrome[a]	Rare 1 (0.01)	**Y** 1 (0.01)	n	**Y**[b] 1 (0.01)
Skin and Subcutaneous Tissue Disorders	Pruritus	Common 658 (7.84)	**Y** 1 (0.01)	n	n
	Rash	Common 580 (6.30)	**Y** 9 (0.10)	n	n
	Dry skin	Common 182 (1.98)	n	n	n
	Rash maculo-papular	Common 182 (1.98)	**Y** 5 (0.05)	n	n
	Vitiligo	Common 99 (1.07)	n	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Erythema	Uncommon 75 (0.81)	n	n	n
	Pruritus generalised	Uncommon 64 (0.69)	**Y** 1 (0.01)	n	n
	Alopecia	Uncommon 60 (0.65)	n	n	n
	Rash pruritic	Uncommon 52 (0.56)	**Y** 1 (0.01)	n	n
	Dermatitis acneiform	Uncommon 48 (0.52)	n	n	n
	Rash macular	Uncommon 45 (0.49)	**Y** 1 (0.01)	n	n
	Urticaria	Uncommon 40 (0.43)	n	n	n
	Rash papular	Uncommon 22 (0.24)	**Y** 2 (0.02)	n	n
	Rash erythematous	Uncommon 21 (0.23)	n	n	n
	Psoriasis	Uncommon 18 (0.20)	**Y** 3 (0.03)	n	n
	Dermatitis	Uncommon 17 (0.18)	n	n	n
	Rash generalised	Uncommon 16 (0.17)	**Y** 1 (0.01)	n	n
	Rash pustular	Uncommon 13 (0.14)	n	n	n
	Erythema multiforme	Rare 7 (0.08)	**Y** 3 (0.03)	n	n
	Dermatitis allergic	Rare 4 (0.04)	n	n	n
	Dermatitis exfoliative	Rare 4 (0.04)	n	n	n
	Stevens Johnson syndrome	Rare 3 (0.03)	**Y** 3 (0.03)	n	n

Table 15.2-1: Adverse Drug Reactions in Patients Treated with Nivolumab Monotherapy in Clinical Studies (N=9,212)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Drug eruption[b]	Rare 2 (0.02)	**Y** 1 (0.01)	n	n
	Rash follicular	Rare 2 (0.02)	n	n	n
	Rash vesicular	Rare 2 (0.02)	n	n	n
	Rosacea	Rare 2 (0.02)	n	n	n
	Toxic epidermal necrolysis	Rare 1 (0.01)	**Y** 1 (0.01)	n	**Y** 1 (0.01)
Vascular Disorders	Hypotension	Uncommon 43 (0.47)	**Y** 5 (0.05)	n	n
	Hypertension	Uncommon 42 (0.46)	n	n	n
	Vasculitis	Rare 2 (0.02)	n	n	n

[a] ADR not included in previous IB version 14.

[b] This event is an adverse drug reaction for nivolumab but serious, related occurrences will be reported as SUSARs due to the low observed frequency.

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Cardiac Disorder	Tachycardia	Uncommon 19 (0.70)	n	n	n
	Atrial fibrillation[a]	Uncommon 7 (0.26)	**Y** 1 (0.04)	n	n
	Myocarditis[a]	Uncommon 4 (0.15)	**Y** 4 (0.15)	**Y** 1 (0.04)	**Y** 2 (0.07)
	Ventricular arrhythmia	Rare 2 (0.07)	**Y** 1 (0.04)	n	n
Ear and Labyrinth Disorders	Vertigo	Uncommon 3 (0.11)	n	n	n
Endocrine Disorders	Hypothyroidism	Common 175 (6.41)	**Y** 8 (0.29)	n	n
	Hyperthyroidism	Common 98 (3.61)	**Y** 14 (0.52)	n	n
	Adrenal Insufficiency	Common 87 (3.21)	**Y** 40 (1.47)	**Y** 1 (0.04)	n
	Hypophysitis	Common 77 (2.84)	**Y** 37 (1.136)	n	n
	Hyperglycaemia	Uncommon 27 (1.00)	**Y** 8 (0.29)	n	n
	Thyroiditis	Uncommon 23 (0.85)	**Y** 6 (0.22)	n	n
	Hypopituitarism	Uncommon 18 (0.66)	**Y** 8 (0.29)	n	n
	Diabetes mellitus	Uncommon 14 (0.52)	**Y** 10 (0.37)	n	n
	Autoimmune thyroiditis	Uncommon 10 (0.37)	**Y** 5 (0.18)	n	n
	Diabetic ketoacidosis	Uncommon 6 (0.22)	**Y** 6 (0.22)	**Y** 1 (0.04)	n
	Autoimmune hypothyroidism	Rare 1 (0.04)	n	n	n
Eye Disorders	Vision blurred	Common 39 (1.44)	**Y** 3 (0.11)	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Uveitis	Uncommon 20 (0.74)	**Y** 3 (0.11)	n	n
	Dry eye	Uncommon 17 (0.63)	n	n	n
	Diplopia	Uncommon 5 (0.18)	**Y** 2 (0.07)	n	n
	Iridocyclitis	Uncommon 3 (0.11)	n	n	n
Gastrointestinal Disorders	Diarrhea	Very Common 555 (20.46)	**Y** 163 (6.01)	**Y** 2 (0.07)	n
	Nausea	Very Common 343 (12.65)	**Y** 24 (0.88)	n	n
	Vomiting	Common 171 (6.31)	**Y** 29 (1.07)	n	n
	Colitis	Common 163 (6.01)	**Y** 119 (4.39)	**Y** 2 (0.07)	**Y** 1 (0.04)
	Abdominal pain	Common 135 (4.98)	**Y** 11 (0.41)	n	n
	Dry mouth	Common 88 (2.99)	n	n	n
	Constipation	Common 57 (2.10)	**Y** 2 (0.07)	n	n
	Stomatitis	Uncommon 26 (0.96)	n	n	n
	Pancreatitis	Uncommon 24 (0.88)	**Y** 18 (0.66)	n	n
	Autoimmune colitis	Uncommon 14 (0.52)	**Y** 13 (0.48)	n	n
	Enterocolitis	Uncommon 10 (0.37)	**Y** 9 (0.33)	n	n
	Mucosal inflammation	Uncommon 9 (0.33)	n	n	n
	Gastritis	Uncommon	**Y**	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		5 (0.18)	2 (0.07)		
	Intestinal perforation[a]	Uncommon 4 (0.15)	**Y** 4 (0.15)	**Y** 2 (0.07)	**Y**[b] 1 (0.04)
	Autoimmune pancreatitis	Rare 1 (0.04)	n	n	n
	Gastritis erosive[b]	Rare 1 (0.04)	**Y** 1 (0.04)	n	n
	Mouth ulceration	Rare 1 (0.04)	n	n	n
General Disorders and Administration Site Conditions	Fatigue	Very Common 589 (21.72)	**Y** 21 (0.77)	n	n
	Pyrexia	Common 269 (9.92)	**Y** 66 (2.43)	n	n
	Chills	Common 109 (4.02)	**Y** 5 (0.18)	n	n
	Asthenia	Uncommon 42 (0.46)	**Y** 5 (0.18)	n	n
	Oedema peripheral	Common 29 (1.07)	n	n	n
	Peripheral swelling	Uncommon 5 (0.18)	n	n	n
	Face oedema	Uncommon 3 (0.11)	n	n	n
	Oedema	Uncommon 3 (0.11	n	n	n
	Periorbital oedema	Uncommon 3 (0.11)	n	n	n
	Localised oedema	Rare 2 (0.07)	n	n	n
	Multi-organ failure[b]	Rare 1 (0.04)	**Y** 1 (0.04)	*n*	**Y** 1 (0.04)
	Swelling face	1 (0.04)	n	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Hepatobilliary Disorders	Autoimmune hepatitis	Common 33 (1.22)	**Y** 19 (0.70)	n	n
	Hepatitis	Uncommon 22 (0.81)	**Y** 18 (0.66)	n	n
	Drug-induced liver injury	Uncommon 7 (0.26)	**Y** 6 (0.22)	n	**Y**[b] 1 (0.04)
	Hyperbilirubinaemia	Rare 3 (0.11)	**Y** 2 (0.07	n	n
Immune System Disorders	Infusion related reaction	Common 39 (1.44)	**Y** 5 (0.18)	n	n
	Hypersensitivity	Uncommon 16 (0.59)	**Y** 2 (0.07	n	n
	Autoimmune disorder	Uncommon 5 (0.18)	**Y** 4 (0.15)	n	n
Infections and Infestations	Bronchitis	Uncommon 6 (0.22)	**Y** 2 (0.07	n	n
Investigations	Alanine aminotransferase increased	Very Common 312 (11.50)	**Y** 75 (2.77)	n	n
	Aspartate aminotransferase increased	Very Common 299 (11.03)	**Y** 54 (1.99)	n	n
	Lipase increased	Common 183 (6.75)	**Y** 11 (0.41)	n	n
	Amylase increased	Common 128 (4.72)	**Y** 6 (0.22)	n	n
	Blood alkaline phosphatase increased	Common 71 (2.62)	**Y** 2 (0.07)	n	n
	Blood creatinine increased	Common 48 (1.77)	**Y** 10 (0.37)	n	n
	Blood bilirubin increased	Common 32 (1.18)	**Y** 8 (0.29)	n	n
	Transaminases increased	Uncommon 29 (1.07)	**Y** 19 (0.55)	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Metabolism and Nutrition Disorders	Decreased appetite	Common 208 (7.67)	**Y** 4 (0.15)	n	n
	Dehydration	Common 60 (2.21)	**Y** 17 (0.63)	n	n
	Hyponatraemia	Common 58 (2.14)	**Y** 21 (0.77)	n	n
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Common 171 (6.31)	**Y** 3 (0.11)	n	n
	Myalgia	Common 103 (3.80)	**Y** 3 (0.11)	n	n
	Back pain	Common 34 (1.25)	n	n	n
	Pain in extremity[b]	Uncommon 17 (0.63)	**Y** 1 (0.04)	n	n
	Arthritis	Uncommon 12 (0.44)	**Y** 4 (0.15)	n	n
	Musculoskeletal pain	Uncommon 8 (0.29)	n	n	n
	Myositis[a]	Uncommon 8 (0.29)	**Y** 6 (0.22)	**Y** 1 (0.04)	**Y** 1 (0.04)
	Neck pain	Uncommon 6 (0.22)	n	n	n
	Polyarthritis	Uncommon 4 (0.15)	n	n	n
	Musculoskeletal chest pain	Uncommon 3 (0.11)	n	n	n
	Bone pain	Rare 2 (0.07)	n	n	n
	Rhabdomyolysis[a]	Rare 2 (0.07)	**Y** 2 (0.07)	**Y** 1 (0.04)	n
	Musculoskeletal discomfort	Rare 1 (0.04)	n	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Nervous System Disorders	Headache	Common 170 (6.27)	**Y** 6 (0.22)	n	n
	Dizziness	Common 55 (2.03)	**Y** 1 (0.05)	n	n
	Neuropathy peripheral	Common 24 (1.44)	**Y** 5 (0.33)	n	n
	Cranial nerve disorder[a]	Uncommon 9 (0.33)	**Y** 5 (0.18)	n	n
	Peripheral sensory neuropathy	Uncommon 9 (0.33)	**Y** 1 (0.04)	n	n
	Encephalitis	Uncommon 5 (0.18)	**Y** 5 (0.18)	n	n
	Meningitis noninfective	Uncommon 5 (0.18)	**Y** 5 (0.18)	n	n
	Peripheral motor neuropathy	Uncommon 5 (0.18)	**Y** 3 (0.11)	n	n
	Meningitis	Uncommon 4 (0.15)	**Y** 4 (0.15)	n	n
	Myasthenia Gravis	Uncommon 3 (0.11)	**Y** 2 (0.07)	n	**Y**[b] 1 (0.04)
	Guillain-Barre Syndrome	Rare 2 (0.07)	**Y** 2 (0.07)	n	n
	Autoimmune encephalitis	Rare 1 (0.04)	**Y** 1 (0.04)	n	n
	Miller Fisher Syndrome[b]	Rare 1 (0.04)	**Y** 1 (0.04)	n	n
	Myasthenic syndrome	Uncommon 1 (0.04)	**Y** 1 (0.04)	n	n
	Polyneuropathy	Rare 1 (0.04)	n	n	n
Renal and Urinary Disorders	Acute kidney injury	Common 29 (1.07)	**Y** 25 (0.92)	**Y** 1 (0.04)	**Y**[b] 1 (0.04)

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Renal failure	Uncommon 7 (0.26)	**Y** 4 (0.15)	n	**Y**[b] 1 (0.04)
	Tubulointerstitial nephritis	Uncommon 5 (0.18)	**Y** 4 (0.15)	n	n
	Autoimmune nephritis	Uncommon 3 (0.11)	**Y** 3 (0.11)	n	n
	Nephritis	Rare 2 (0.074)	**Y** 2 (0.07)	n	n
	Nephritis allergic[b]	Rare 2 (0.07)	**Y** 1 (0.04)	n	n
Respiratory, Thoracic, and Mediastinal Disorders	Pneumonitis	Common 132 (4.87)	**Y** 70 (2.58)	**Y** 1 (0.04)	**Y** 5 (0.18)
	Cough	Common 95 (3.50)	n	n	n
	Dyspnea	Common 80 (2.95)	**Y** 17 (0.63)	n	n
	Lung infiltration	Uncommon 5 (0.18)	**Y** 2 (0.07)	n	n
	Respiratory failure	Uncommon 5 (0.18)	**Y** 4 (0.15)	n	**Y** 2 (0.07)
	Respiratory distress	Uncommon 3 (0.11)	**Y** 3 (0.11)	n	n
	Interstitial lung disease	Rare 1 (0.04)	n	n	n
Skin and Subcutaneous Tissue Disorders	Pruritus	Very Common 405 (14.93)	**Y** 2 (0.07)	n	n
	Rash	Common 340 (12.54)	**Y** 12 (0.44)	n	n
	Rash maculo-papular	Common 201 (7.41)	**Y** 4 (0.15)	n	n
	Rash pruritic	Common	n	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		70 (2.58)			
	Dry skin	Common 50 (1.84)	n	n	n
	Vitiligo	Common 49 (1.81)	n	n	n
	Alopecia	Common 28 (1.03)	n	n	n
	Rash generalised	Common 28 (1.03)	n	n	n
	Dermatitis acneiform	Uncommon 24 (0.88)	n	n	n
	Rash macular	Uncommon 24 (0.88)	n	n	n
	Erythema	Uncommon 20 (0.74)	n	n	n
	Pruritus generalised	Uncommon 19 (0.70)	n	n	n
	Rash papular	Uncommon 19 (0.70)	n	n	n
	Rash erythematous	Uncommon 13 (0.48)	n	n	n
	Dermatitis	Uncommon 11 (0.41)	Y[b] 1 (0.04)	n	n
	Urticaria	Uncommon 10 (0.37)	n	n	n
	Rash pustular	Uncommon 7 (0.26)	n	n	n
	Psoriasis	Uncommon 5 (0.18)	n	n	n
	Erythema multiforme	Uncommon 3 (0.11)	n	n	n
	Rash follicular	Uncommon 3 (0.11)	n	n	n

Table 15.2-2: Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=2,712)

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Dermatitis exfoliative	Rare 2 (0.07)	**Y**[b] 1 (0.04)	n	n
	Rosacea	Rare 2 (0.07)	n	n	n
	Stevens-Johnson Syndrome	Rare 1 (0.04)	**Y** 1 (0.04)	**Y** 1 (0.04)	n
	Toxic Epidermal Necrolysis	Rare 1 (0.04)	**Y** 1 (0.04)	n	**Y** 1 (0.04)
Vascular Disorders	Hypotension[a]	Common 29 (1.07)	**Y** 9 (0.33)	**Y**[b] 1 (0.05)	n
	Hypertension	Uncommon 16 (0.59)	n	n	n

[a] ADR not included in previous IB version 14.

[b] This event is an adverse drug reaction for nivolumab but serious, related occurrences will be reported as SUSARs due to the low observed frequency.

15.3 Management of Immune-related Adverse Events

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

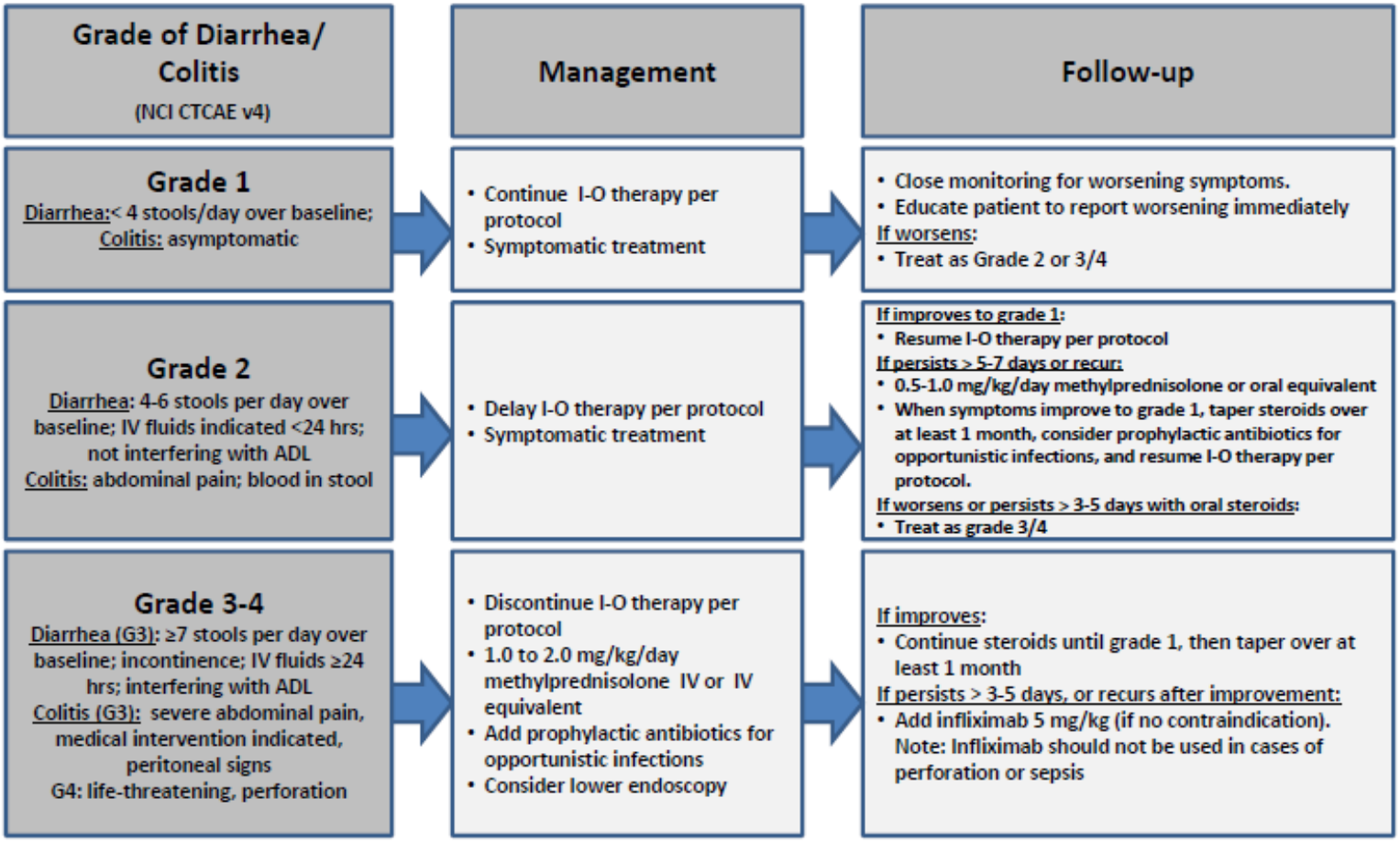
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

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.

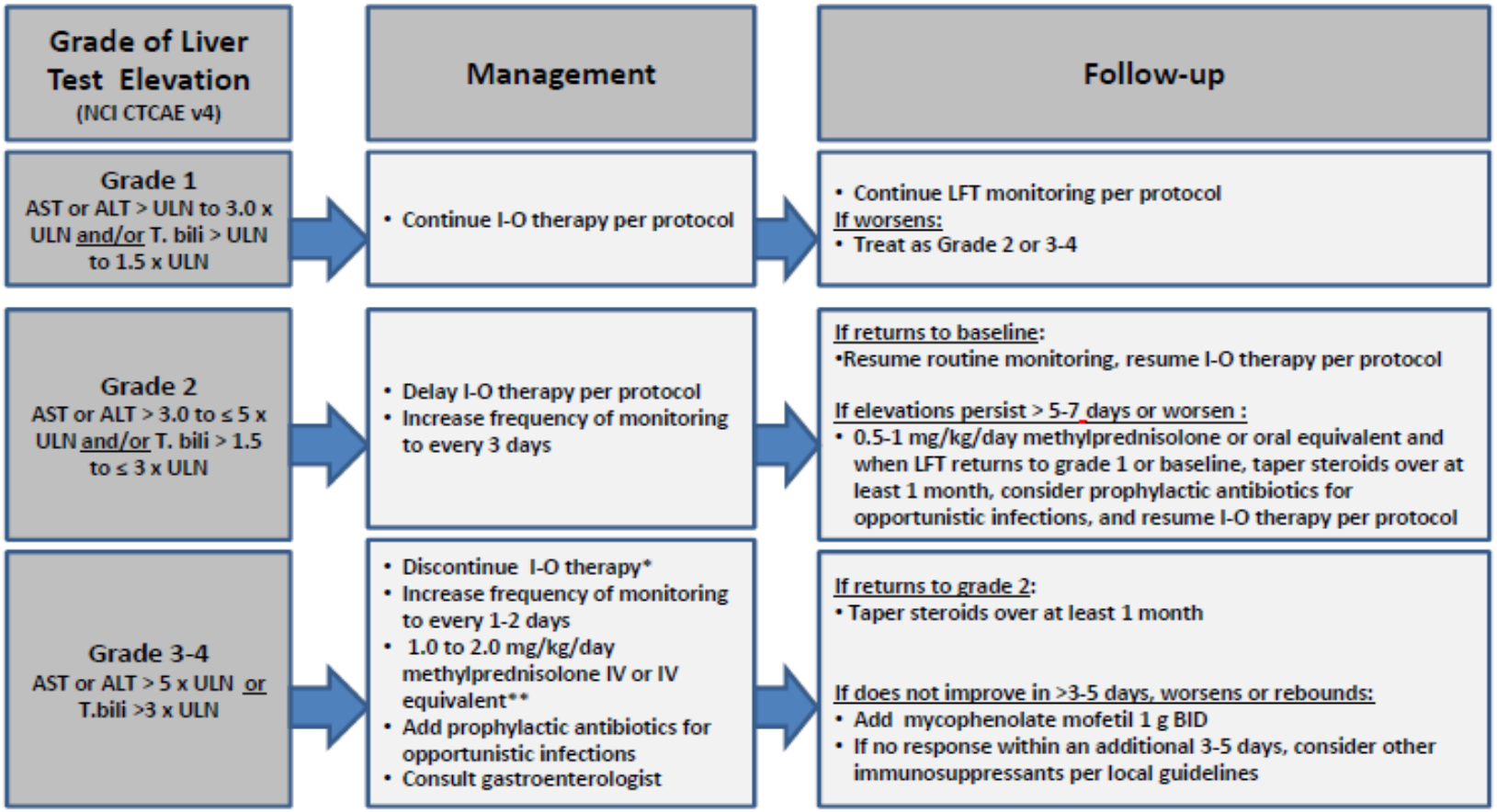


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

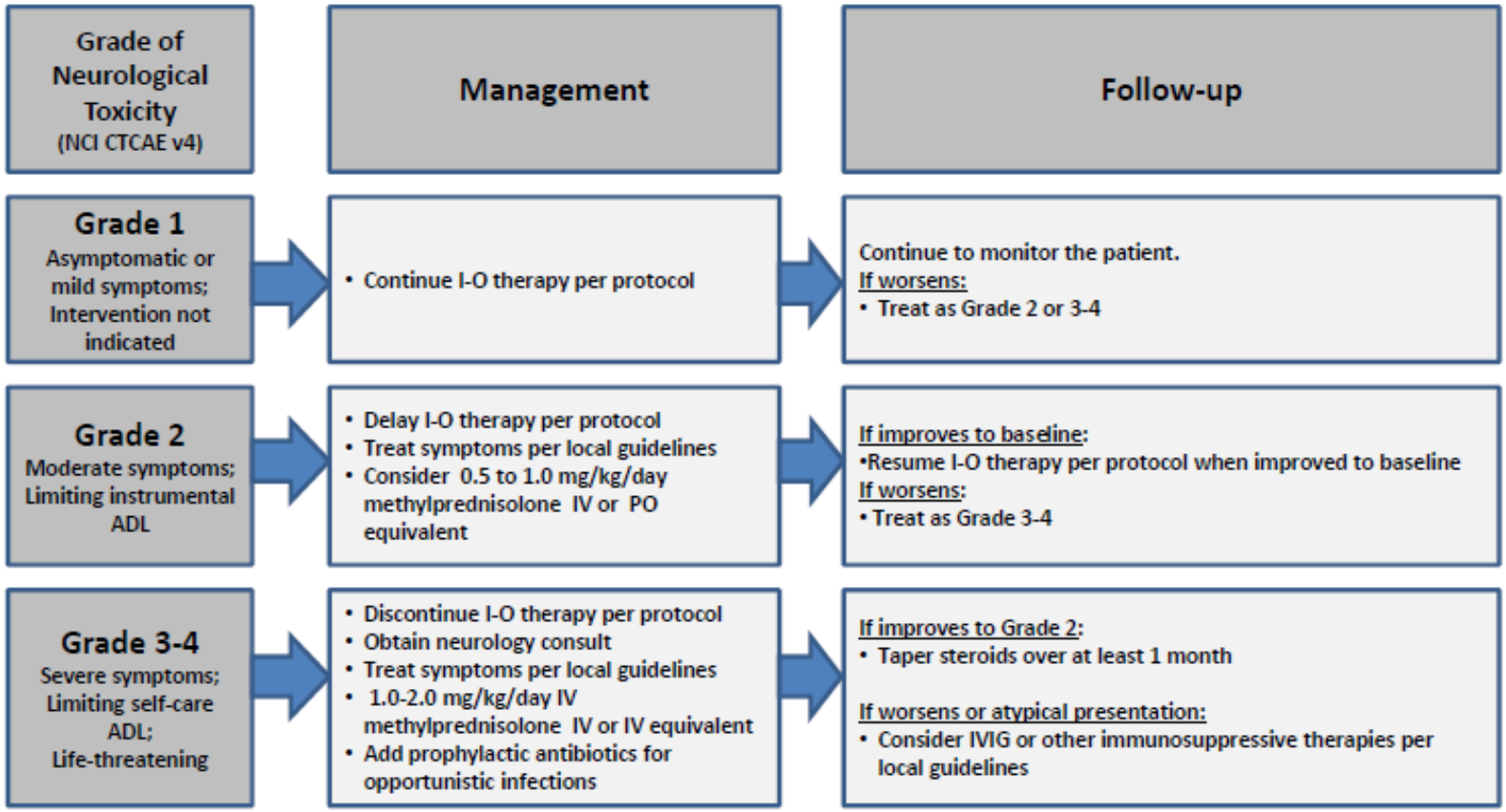
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

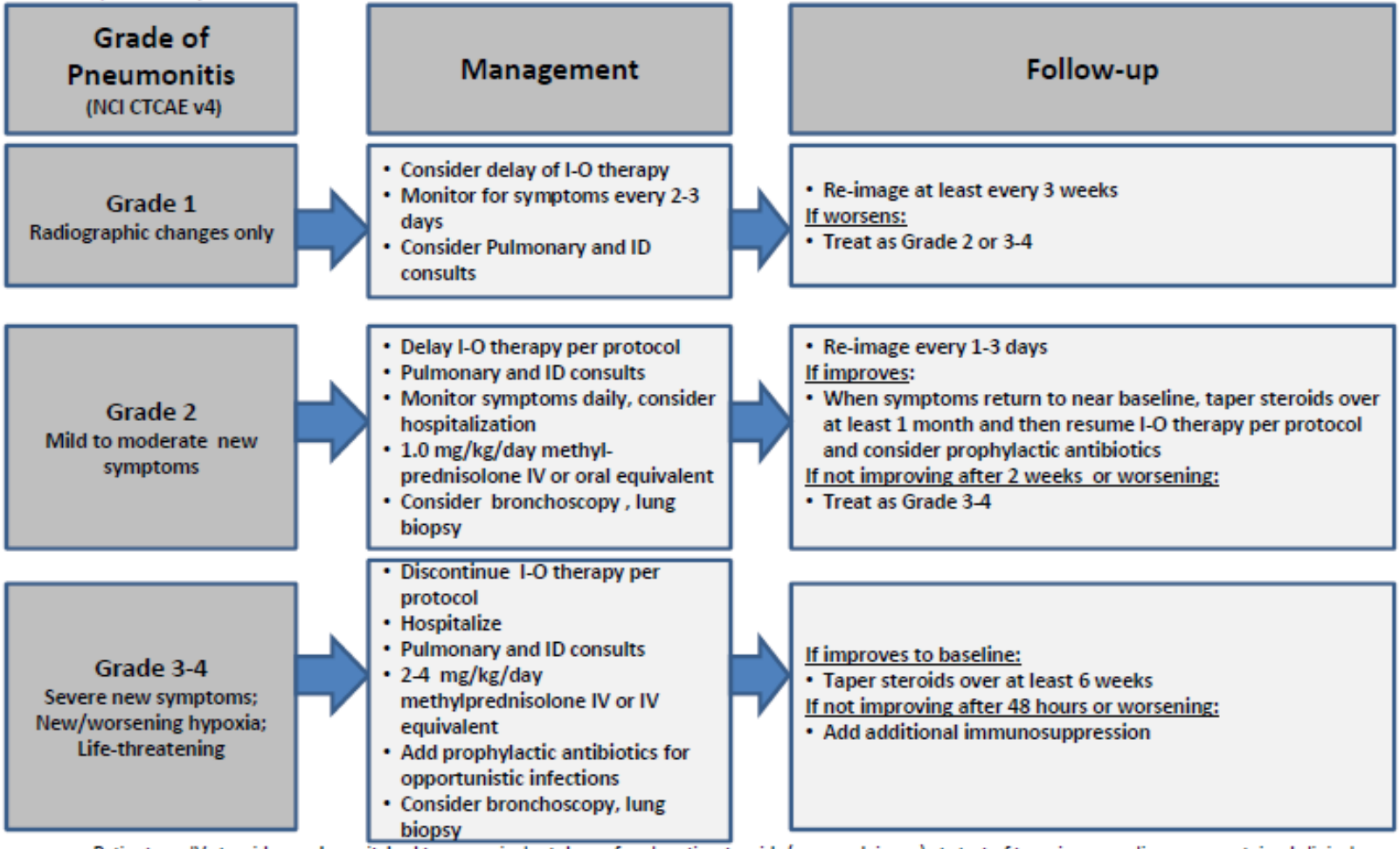


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

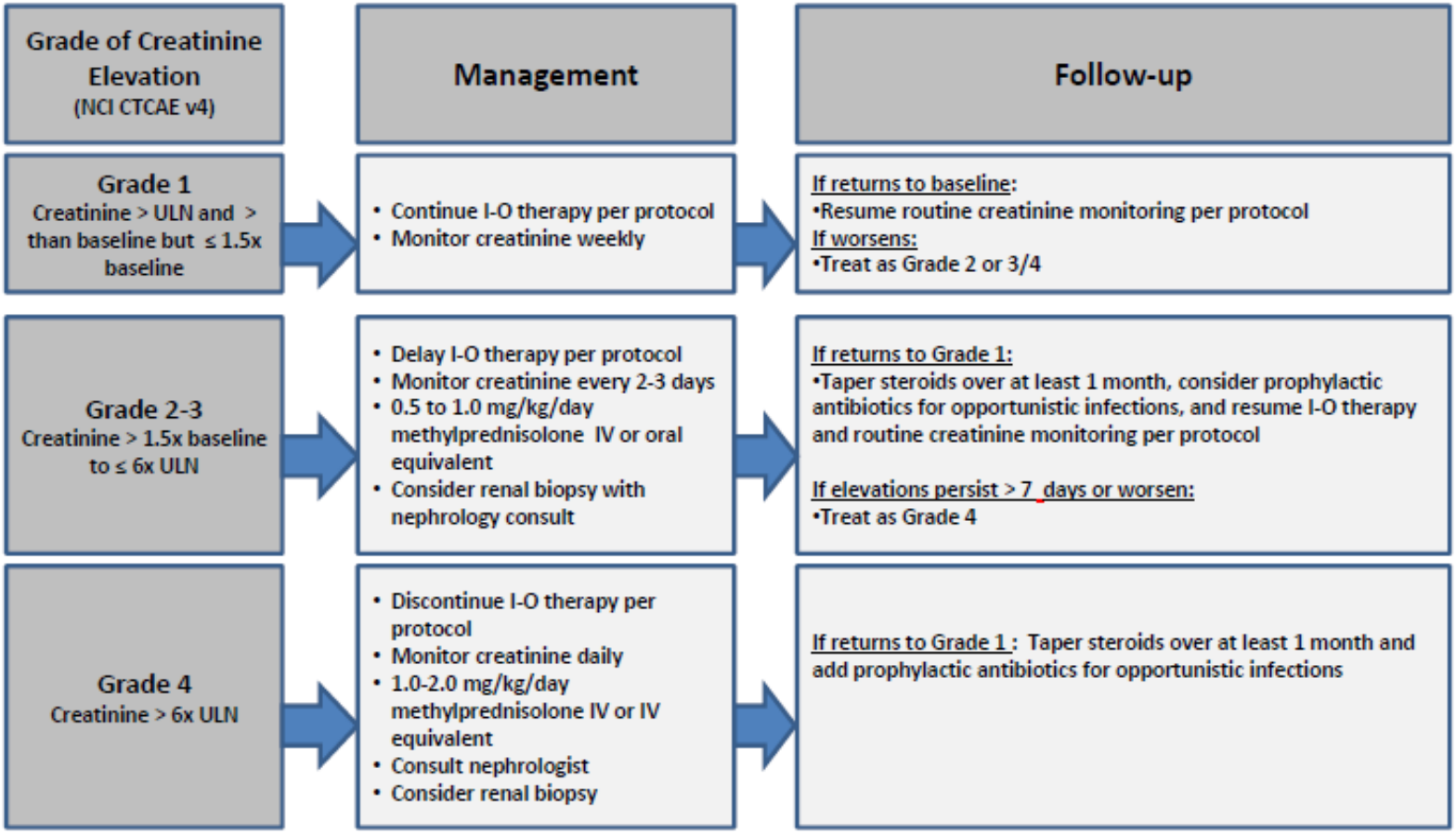


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

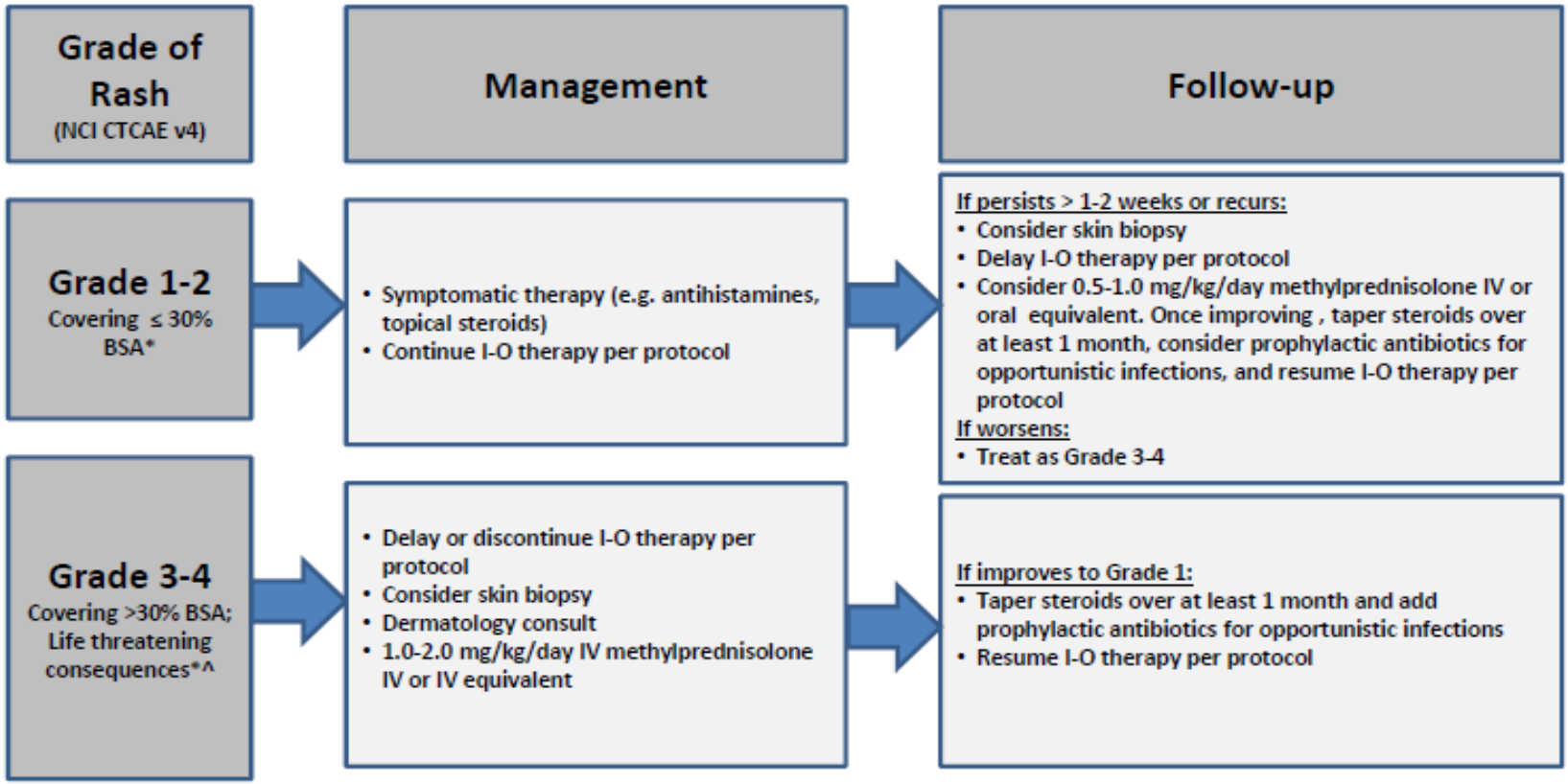


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

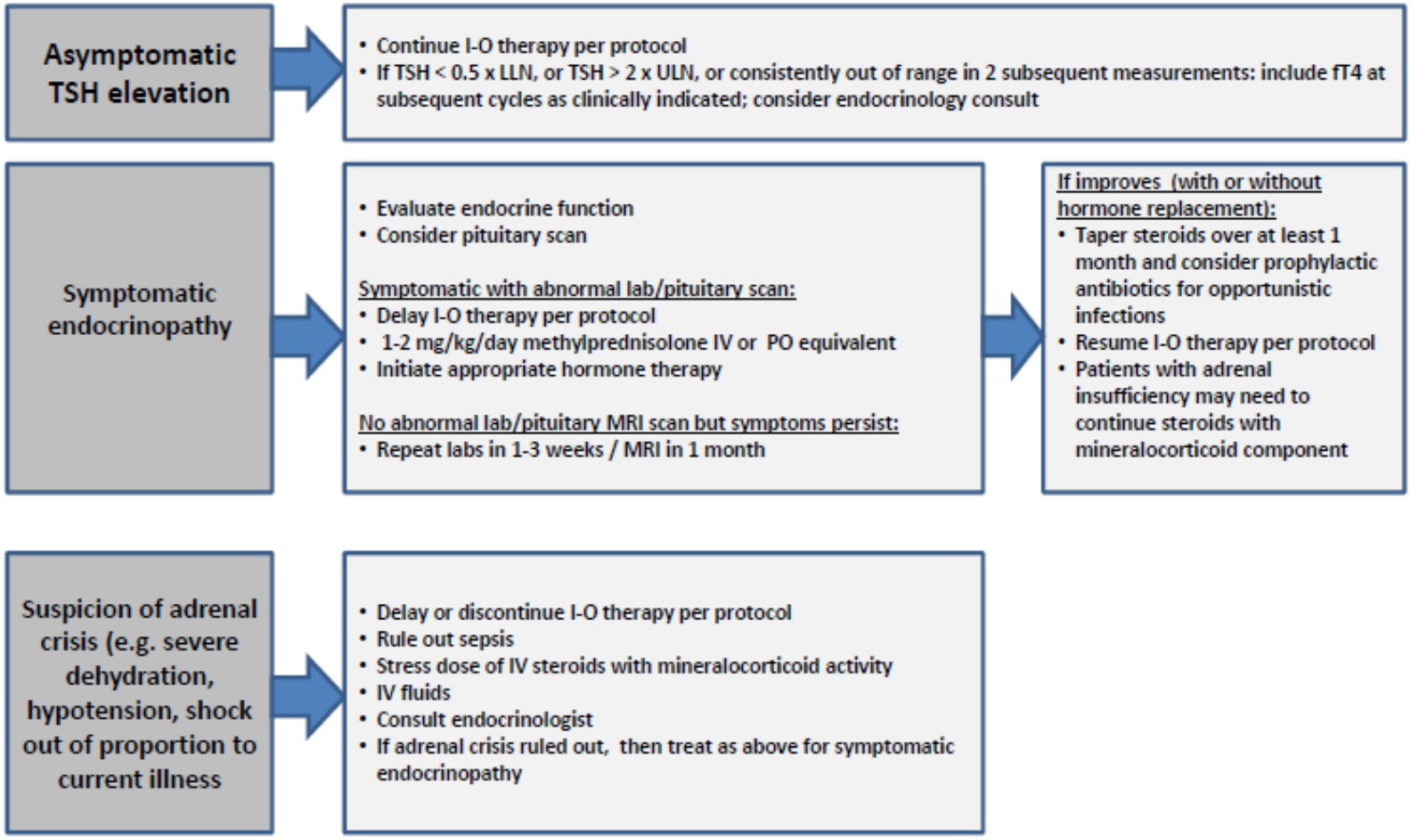
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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



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

Updated 05-Jul-2016

15.4 PROTOCOL REVISION HISTORY

Version 3: 25FEB2019

Title Page: Co-Investigator change; delete Ryan Weight, DO; add Melissa Wilson, MD, PhD

Section 1.0: Introduction: eliminate study objectives (redundant with Section 2)

Section 3.1: General Design:

- specify that in event of toxicity during first four IPI + NIVO + IEMBO cycles, administration of IPI may be halted and patient may continue with NIVO + IEMBO
- clarify that initial radiographic scans will be performed between Cycles 2 and 3 to ensure no rapid disease progression
- clarify that initial radiographic response will be determined following all 4 doses of IPI + NIVO (and/or NIVO alone, if IPI is halted) and four IEMBO treatments (also Section 9.1)

Section 3.2: Primary Study Endpoint: clarify that primary endpoint is Best Hepatic Response starting at Week 12

Section 5.3.3: Embolization: specify that interval between immunoembolization treatments may be extended for up to 6 weeks at the disecretion of treating physician

Section 5.6: Prior and Concomitant Therapy: add that palliative radiation is allowed during treatment and that bone strengthening agents are allowed for bone metastases

Sections 6.0: Study procedures:

- 6.1.1, 6.1.2: added blood test for CRP; clarified timing of certain blood tests
- 6.1.4:
    - clarify that end of fourth cycle = 12 weeks from start of treatment
    - clarify that patients who have unequivocal disease progression after 4 treatments may be removed from study at discretion of investigator and that patients will then be followed in person or over telephone every 3 months until death.
    - Clarify that if a mixed response is seen at interim 6 week scans, patients may be allowed to continue on study if investigator deems they are getting clinical benefit

Section 8.0: Safety and Adverse Events:

- sections cleaned up and re-numbered
- 8.3: added section on adverse event reporting

Section 9.0: Evaluation of Response: sections cleaned up and re-numbered

Section 15.4: Protocol Revision History: add this section

Version 4: 23OCT2019

Title Page: Co-Investigator updates

Study Summary; Study Design (sec. 3.1); Study Procedures (sec. 6.1.4); Dose Delays and Dose Modifications (sec. 6.3.3); Statistical Plan (sec. 7.2.1); Evaluation of Response (sec. 9.1): Clarification of investigator's discretion to halt immunotherapy (ipilimumab and/or nivolumab) components of treatment in instances of toxicity and continuing treatment with immunoembolization alone if patient is receiving clinical benefit.

Version 5: 22DEC2019

Section 4.2: Exclusion criteria (#3): clarification that liver resection and focal ablation are permitted

Version 6: 17MAR2020

Study Summary and General Study Design (sec.3.1):

- Clarify on-treatment radiographic scans will be performed after evert two IEMBO treatments
- Specify subjects will receive study treatment for a maximum of two years or until disease progression
- Clarify that combination treatment postponement duration begins from date of next scheduled treatment

Section 3.4: Exploratory (Correrlative) Endpoints : Add changes in PBMC cell populations, including T cells and MDS

Section 4.2: Exclusion Criteria: delete exclusion criteria #6 and #15: requirement of angiography

Section 4.2.1: Guidance for Women of Childbearing Potential: clarify that pregnancy testing must occur within two weeks prior to the start of treatment

Section 5.6: Prior and Concomitant Therapy: Add information about a washout period between certain prior therapies and first study treatment cycle

Section 6.1.2: Evaluation during treatment: Add information about time points for collection of blood for lab tests

Section 6.1.6: Completion of Study:

- Specify subjects will receive study treatment for a maximum of two years or until disease progression

- Add research-related testing to end of study procedures

Section 6.3: Dose Delays and Modifications: Clarify that combination treatment postponement duration begins from date of next scheduled treatment

Section 9.1: Evaluation of Clinical Response: Clarify patients who are evaluable for clinical response

Section 9.4: Evaluation of Overall Response in Liver Metastases: Clarify on-treatment radiographic scans will be performed after every two IEMBO treatments

Version 7: 01SEP2020

Section 5.1.4: Ipilimumab: Clarify that IV infusion of ipilimumab is done over 30 minutes with a +/- 5 minute window

Section 5.1.5: Nivolumab: Clarify that IV infusion of nivolumab is done over 30 minutes with a +/- 5 minute window

Section 6.1: Study Visit Schedule: Clarify that all CT scans of the chest are done without use of contrast

Section 11.3: Data Collection: Specify that the Redcap database (rather than standard case report forms) will be the primary data collection instrument for the study