# Adjuvant Nivolumab and Low Dose Ipilimumab for Stage III and Resected Stage IV Melanoma: A Phase II Brown University Oncology Research Group Trial

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## 1.0 OBJECTIVES

### 1.1 Primary Objective

1.1.1. To evaluate the toxicity of nivolumab and low-dose ipilimumab as adjuvant therapy for patients with high risk melanoma.

1.1.2 To evaluate the recurrence-free and survival overall following adjuvant nivolumab and low dose ipilimumab for patients with high risk melanoma.

### 1.2 Secondary Objective

1.2.1 To evaluate what percentage of patients are able to complete the planned 6 months course of treatment without toxicities requiring discontinuation.

## 2.0 BACKGROUND

**Melanoma:** Malignant melanoma is the most common fatal form of skin cancer.[1] There were 76,100 new cases of melanoma last year and 9,710 deaths.[2] There are important, preventable environmental risk factors for melanoma such as sun and ultraviolet ray exposure.[3,4] Individuals traits such as light skin pigmentation, hair color (red or blond), high-density freckling, and light eye color (green, hazel, blue) are also associated with increased risk. Genetic features, such as hereditary p16 gene abnormalities, account for about 10% of melanoma.[5]

**Adjuvant Therapy for Melanoma:** The curative modality for early stage melanoma is surgical resection. Unfortunately, some patients will subsequently relapse with metastatic disease that is generally fatal. High-risk features in the primary tumor define subsets that are at increased risk for recurrent disease.[6] Patients with a deep primary tumor (> 4mm or involved regional lymph nodes have a risk of relapse and death of > 50%. [7,8]

Agents evaluated in the adjuvant setting include chemotherapy such as dacarbazine, nonspecific immune adjuvants such as Bacillus Calmette-Guerin (BCG) vaccine, Corynebacterium parvum and levamisole, and hormonal agents such as megace. However, none of these agents have shown benefit in preventing recurrence in randomized trials.[9-11]

**Adjuvant Interferon:** Interferon alfa appears to be an active agent in melanoma by stimulating the immune system against melanoma. [12,13] The phase Eastern Cooperative Oncology Group (ECOG) trial ECOG 1684, demonstrated that adjuvant interferon prolongs disease-free and overall survival in selected patients at increased risk for disease dissemination. Two-hundred eighty seven patients with melanomas >4 mm in depth (stage IIB) or subclinical or clinically apparent regional node involvement (stage III) were randomly assigned to one year of high-dose (HD) IFNa-2b or observation. [14] Interferon treatment consisted of intravenous therapy at a dose of 20 million units/$m^2$ five days per week for four weeks followed by 10 million units/$m^2$ subcutaneously three times weekly for an additional 11 months. Treatment with interferon demonstrated a nine-month prolongation in relapse-free survival and a one-year prolongation in median survival (3.8 versus 2.8 years). However, in a subsequent analysis, the improvement in overall survival was no longer statistically significant. [15] Furthermore in a phase III study

of pegylated interferon, a survival benefit was not seen. [16] Treatment benefit with high dose interferon appears to be confined to patients with lymph node involvement as well as those with stage T4B (>4mm primary tumor with ulceration). High dose interferon is associated with numerous adverse effects, including acute constitutional symptoms, chronic fatigue, myelosuppression, thyroid abnormalities and neurologic and psychological effects, which are experienced by the majority of patients. In particular, fatigue is common and was present in 70 to 100 percent of patients in large trials. Fatigue can increase in severity with duration of therapy and can be debilitating. Mild to moderate depression and impaired cognitive function are commonly reported.

**Immune Checkpoint Inhibitors:** The immune checkpoint inhibitors are the most important new class of agents in the treatment of advanced melanoma. The immune system can be enhanced to vigorously attack melanoma by turning off important immune system inhibitory pathways including the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathway and the programmed death 1 (PD-1) pathway. [17]

Ipilimumab, an anti–cytotoxic T-lymphocyte– associated antigen 4 (CTLA-4) antibody, acts to up-regulate antitumor immunity and was the first agent to be associated with an improvement in overall survival in a phase 3 study involving patients with metastatic melanoma.[17,18] Ipilimumab was associated with responses in 10% and 15% of patient;[17,18] approximately 20% of treated patients had long-term survival.[19,20]

Two anti–programmed death 1 (PD-1) antibodies, nivolumab and pembrolizumab, were approved by the Food and Drug Administration in 2014 for the treatment of metastatic melanoma after progression during ipilimumab treatment and, in patients with BRAF-mutated melanoma, after progression during treatment with a BRAF inhibitor.[20-24] These antibodies were associated with objective responses in 30 to 40% of patients, with the majority of responses being durable. Two phase 3 trials have shown superior efficacy of nivolumab, as compared with chemotherapy, in previously untreated patients with wild-type BRAF tumors[21] or in patients with either mutant or wildtype BRAF tumors after progression during ipilimumab therapy and, in patients with tumors positive for BRAF mutation, after progression during treatment with a BRAF inhibitor.[22] Similar results were observed in a phase 2 trial of pembrolizumab versus chemotherapy.[23] Recently, pembrolizumab was associated with longer progression-free survival and overall survival and higher response rates than those associated with ipilimumab in a phase 3 trial involving patients with advanced melanoma.[24]

**Ipilimumab and Nivolumab Is the Most Active Regimen In Advanced Melanoma:** A phase III study, Checkpoint 067, showed that the combination of ipilimumab and nivolumab is more active in advanced melanoma that either agent alone. In this trial 945 previously untreated patients with unresectable stage III or IV melanoma were randomly assigned 1:1:1 to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab. The median progression-free survival was 11.5 months (95% confidence interval [CI],8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI,2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). In patients with tumors positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the

nivolumab group, but in patients with PD-L1–negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group. The most common adverse events in the nivolumab-plus-ipilimumab group were diarrhea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%).

**Adjuvant High Dose Ipilimumab:** Adjuvant high dose (10mg/kg) ipilimumab is being evaluated as an adjuvant in patients at high risk of relapse after initial definitive therapy. In the EORTC 18071 trial, 951 patients were randomly assigned to either ipilimumab or placebo.[26] All patients had stage III melanoma, and 80 percent had stage IIIB or IIIC disease. The other 20 percent had stage IIIA disease with melanoma >1 mm diameter in the sentinel lymph node. Treatment with ipilimumab was given at a dose of 10 mg/kg every three weeks for four doses, then every three months for three years unless toxicity or relapse prevented its continuation. Placebo was given on the same schedule. The primary endpoint of the trial was relapse-free survival. The median recurrence-free survival (RFS) was significantly increased with ipilimumab compared with placebo (median 26 versus 17 months, three-year RFS 46.5 versus 34.8 percent, hazard ratio [HR] 0.75, 95% CI 0.64-0.90). Toxicity associated with adjuvant ipilimumab was quite significant. Immune-related side effects were observed in 90 percent of patients treated with ipilimumab, including 36.5 with grade 3 events, and 5.5 percent with grade 4 events. The most common treatment-related adverse events were dermatologic, gastrointestinal, endocrine, and hepatic (63, 46, 38, and 25 percent of patients, respectively). Primarily because of toxicity, only one-half of the patients assigned to ipilimumab received more than the initial 12 weeks of therapy and only 29 percent of the patients remained on therapy beyond one year. There were five treatment-related deaths (three due to colitis, one to myocarditis, and one due to multiorgan failure with Guillain-Barre syndrome) in patients treated on the ipilimumab arm.

**Low Dose Ipilimumab:** Wolchok et al evaluated 217 patients over three dose levels of single agent ipilimumab at doses of 10mg/kg, 3mg/kg and 0.3 mg/kg. Response rates were 11%, 4.2% and 0%, respectively.[27] However, prolonged stable disease was seen at all 3 dose levels. At the lowest dose level biologic effect was observed with grade 1 and grade 2 toxicities but no grade 3 toxicities. The absolute lymphocyte count was similar in the 0.3 and 3mg/kg doses but lower than the 10mg/kg dose. Praeto performed a series of protocols with a combination of ipilimumab with other immunologic agents including the gp100 vaccine and IL-2.[28] Ipilimumab doses were 0.1, 0.3, 1, 2 and 3mg/kg IV every 3 weeks. Interestingly, among the most active and best tolerated arms was 1mg/kg ipilimumab (after an initial 3mg/kg bolus dose). Two patients in this protocol treated with 1mg/kg had a continuous complete response with the combination of ipilimumab 1mg/kg and the gp100 vaccine for 94 and 88 months.

**Single Agent Nivolumab and in Combination with Ipilimumab in Non-Small Cell Lung Cancer (NSCLC):** Nivolumab is FDA approved for treatment of advanced NSCLC. In the initial expanded phase I study a total of 122 patients with NSCLC were enrolled.[29] Patients were heavily pretreated with 55% of patients receiving at least three prior lines of therapy. Results showed 15 percent of participants experienced a partial response, of whom 59 percent had response durations of six months or

longer. Nivolumab is FDA approval to treat metastatic squamous cell lung cancer with progression on or after first-line chemotherapy based on Checkmate 017.[30] Patients receiving nivolumab experienced improved survival and less toxicity as compared with standard second line chemotherapy with docetaxel. Nivolumab has also been FDA approved in second line non-squamous cell lung cancer based on Checkmate 057. The 12-month overall survival was 51% for nivolumab compared with 39% for docetaxel. [31] The response rate was 19% for nivolumab versus 6% for docetaxel. Grade 3/4 toxicities were higher with docetaxel (20% versus 7%).

**Nivolumab In Combination With Ipilimumab in NSCLC:** CheckMate 012 compared several dosing schedules of nivolumab and ipilimumab for frontline treatment of advanced NSCLC as follows:[32]

- Nivolumab at 1mg/kg every 3 weeks x 4 plus ipilimumab at 1mg/kg every 3 weeks x 4 followed by nivolumab at 3mg/kg every 2 weeks (n=31).
- Nivolumab at 1mg/kg every 2weeks plus ipilimumab at 1mg/kg every 6 weeks (n=40).
- Nivolumab at 3mg/kg every 2 weeks plus ipilimumab at 1mg/kg every 12 weeks (n=38)
- Nivolumab at 3mg/kg every 2 weeks plus ipilimumab at 1mg/k every 6 weeks (n=39).

Grade 3/4 treatment related adverse events occurred in 28-35% of patients and only 3-10% of patients discontinued therapy. Thus the toxicity of low dose ipilimumab appears substantially reduced. Objective responses were confirmed in 13-39% of patients with the highest responses rates in the cohorts receiving nivolumab 3mg/kg every 2 weeks plus ipilimumab at 1mg/kg every 6-12 weeks.

**Protocol Rationale:** Effective adjuvant treatment can increase cure in patients with high-risk resected melanoma. High dose interferon is a standard of care in the adjuvant setting but is highly toxic and marginally effective. The combination of ipilimumab and nivolumab is the most active regimen in patients with advanced melanoma so there is clear rationale to test this regimen in the adjuvant setting. The M.D. Anderson Cancer Hospital will be testing adjuvant ipilimumab 3mg/kg and with nivolumab 1mg/kg followed by 3mg/kg maintenance (NCT02519322). This regimen is expected to be quite toxic and initially uses low dose of nivolumab – the more active immune checkpoint inhibitor. Praeto et al demonstrated that lower dose ipilimumab can be safely combined with other immunologic agents with important biologic activity.[28] For example, two patients treated in the Praeto study at the 1mg/kg maintenance dose level of ipilimumab had prolonged complete responses. In the study by Rizvi et al in NSCLC, the regimen of nivolumab 3mg/kg every 2 weeks with ipilimumab 1mg/kg every 6-12 weeks appears to be the most promising for further investigation Therefore we will investigate nivolumab 3mg/kg every 2 weeks with 1mg/kg ipilimumab every 6 weeks in the high risk adjuvant setting. The duration of therapy will be six months to be consistent with the M.D. Anderson protocol of 6 months of adjuvant ipilimumab 3mg/kg and nivolumab 3mg/kg.

## 3.0 PATIENT ELIGIBILITY

### 3.1 Conditions for patient eligibility

3.1.1. Histologically or cytologically proven melanoma. The primary site of melanoma may be cutaneous or other body site such as ocular or anorectal. Documentation required to be sent to BrUOG.
3.1.2 Completely resected stage III (patients cannot be N0) or resected stage IV disease. Patients with stageT4BN0 are also eligible. Documentation of resection with pathology report to be sent to BrUOG. It is required that patients with stage IIIA disease have > 1mm nodal involvement via pathology assessment of the resected node. All patients must be disease free to be eligible. Confirmation to be sent to BrUOG.
3.1.3: No prior treatment for melanoma other than surgical resection or radiation. At least 4 weeks since prior surgery and 3 weeks since prior radiation to registration date.
3.1.4: Age >/= 18 years
3.1.5: ECOG performance status 0-1
3.1.6 Patients must have organ and marrow function as defined below within 14 days of study entry:
Hematologic Absolute neutrophil count (ANC) >/= 1.5 X $10^9$/L;
Hemoglobin >/= 9.5 g/dL;
Platelets >/= 100 X $10^9$/L;
Total Bilirubin ≤ 1.5 x ULN except subjects with normal direct bilirubin or those with known Gilbert's syndrome. Send information to BrUOG if patient has known Gilbert's syndrome
AST and ALT </= 2.5 X ULN
Albumin >/= 2.5 g/dL
Renal Creatinine OR Calculated creatinine clearance : Creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 50ml/min
3.1.7 No clinically significant coagulation disorder as defined by the treating MD. Therapeutic use of anticoagulants is permissible. Add to concomitant medication log if applicable.
3.1.8. Not pregnant and not nursing. Women of child bearing potential must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to Day 1 of treatment. Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, please document status.
3.1.9 Confirmation of informed consent.
3.1.10 Men and women of childbearing potential enrolled in this study must agree to use adequate barrier birth control measures during the course of the study and for 2 months after end of treatment.

### 3.2 Exclusion Criteria:

3.2.1 Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) or investigational anti-cancer drug
3.2.2 Brain metastases, whether resected or not, and any known leptomeningeal disease or known bone metastases. To confirm in writing to BrUOG.
3.2.3 Pregnant or breastfeeding female. If lactating, must have documentation in writing that patient will not breastfeed from time of consent through 2 months post the last dose of drug.
3.2.4 Unwillingness or inability to follow the procedures required in the protocol, to document
3.2.5 Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

3.2.6 Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. Documentation required to be sent to BrUOG
3.2.7 Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, controlled type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
3.2.8 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10mg daily of prednisone equivalents are permitted in the absence of active autoimmune disease.

3.2.9 Prior treatment with an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody
3.2.10 Any positive test result for hepatitis B or C virus indicating acute or chronic infection
3.2.11 Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome
3.2.12 History of severe hypersensitivity reaction to any monoclonal antibody. To confirm if applicable in writing to BrUOG
3.2.13 Patients with unstable angina (anginal symptoms at rest) or new-onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.
3.2.14 History of autologous transplant or organ allograft even if not taking immunosuppressive medications

**4.0 TREATMENT**
**4.1 Schema:**
**Nivolumab and Ipilimumab:** 1 cycle = 6 weeks (+/- 8 days) (coinciding with receipt of Ipilimumab). Patients will receive 4 cycles of therapy

Ipilimumab:1mg/kg q6weeks (1 dose per cycle, 4 planned treatments over 6 months total)
Nivolumab:
Patients who were enrolled and began treatment before Amendment # 2 was IRB approved: Nivolumab: 3mg/kg q2weeks (+/-3 days) (3 doses per cycle, 12 planned treatments over 6 months total)
Patients enrolled and who start treatment (cycle 1) based on Amendment #2: Nivolumab: 3mg/kg up to a total a total of 240mg IV over approximately 60 minutes (+/- 3 days) (3 doses per cycle, 12 planned treatments over 6 months total)

Doses do not need to be recalculated if weight change is less than 10% of total body weight, as per institutional standard practice.
(In general, when both drugs are due on the same day, it is suggested that ipilimumab be given prior to nivolumab, but the study does allow for the reverse to occur if for whatever reason it is more convenient and this will not be considered a deviation.)

Cycles are every 6 weeks (+/- 8 days) however, it will not be considered a deviation if a cycle or pre-treatment assessments must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG.

## 5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 4

### 5.1 Dose Modifications:

No dose reductions of nivolumab or ipilimumab are included in the study.

### 5.2 The following must be confirmed prior to dosing a patient with nivolumab and ipilimumab:

1) Patients experiencing treatment related (drug) grade 4 or treatment related (drug) clinically significant grade 3 toxicities must have toxicity resolved to grade 2 or less prior to resuming nivolumab and ipilimumab.

### Adverse event management table:

| Event | Issue | Action |
|---|---|---|
| Labs: | 1) AST or ALT >3 to 5 times ULN (grade 2) or total bilirubin >1.5 to 3 times ULN (grade 2)<br><br>2) AST or ALT >5 times ULN (grade 3) or total bilirubin >3 times ULN (grade 3) | 1) **Hold treatment until recovery to grade 1 or resolution. Withhold treatment;** may resume therapy upon recovery to grade 0 or 1 toxicity (AST/ALT grade 1 is >ULN-3xULN, Total bilirubin grade 1 is >ULN-1.5xULN).<br><br>2) **Permanently discontinue.** |
| Immune mediated hepatitis: | 1) Grade 2 or higher transaminase elevations that are possibly, probably or definitely related to nivolumab or ipilimumab (with or without total bilirubin elevations)<br>• AST or ALT >3 to 5 times ULN (grade 2)<br>• Total bilirubin >1.5 to 3 times ULN (grade 2)<br><br>2) Severe (grade 3) or life-threatening (grade 4) transaminase elevations | 1) **Hold treatment until recovery to grade 1 or resolution and** Withhold treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)<br><br>2) Permanently discontinue treatment and initiate high-dose |

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| | | systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)<br>**document on conmed log* |
| Kidney | 1) Creatinine >1.5 to 6 times ULN (grade 2 or 3) or >1.5 times baseline (grade 1) | 1) **Hold treatment until recovery to grade 1 or resolution.** Withhold treatment; administer prednisone 0.5 to 1 mg/kg daily (or equivalent) followed by a corticosteroid taper; may resume therapy upon recovery to grade 0 or 1 toxicity. If toxicity worsens or does not improve, permanently discontinue and increase corticosteroid dose to prednisone 1 to 2 mg/kg daily (or equivalent).<br>**document on conmed log* |
| | 2) Creatinine >6 times ULN (grade 4) | 2) Permanently discontinue; initiate high-dose systemic corticosteroids<br>**document on conmed log* |

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|---|---|---|
| Colitis | 1) Grade 2 (duration >5 days) | 1) **Hold treatment until recovery to grade 1 or resolution.** Also administer systemic corticosteroids (prednisone 0.5 to 1 mg/kg daily or equivalent) followed by a corticosteroid taper; may increase to prednisone 1 to 2 mg/kg daily (or equivalent) if colitis worsens or does not improve despite corticosteroid use<br>**document on conmed log* |
| | 2) Grade 3 | 2) Permanently discontinue drugs. Also administer systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper<br>**document on conmed log* |
| | 3) Colitis: (grade 4) | 3) Permanently discontinue drugs. Also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper |
| | 4) Colitis (recurrent) | 4) Permanently discontinue drugs |
| Lung | 1) Pneumonitis (grade 2) | 1) **Hold treatment until recovery to grade 1 or resolution**. also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper<br>**document on conmed log* |
| | 2) Pneumonitis (grade 3 or 4); | 2) Permanently discontinue. |

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| | | also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper |
| Immune mediated | 1) immune mediated toxicity | 1) **Hold treatment for all grade 2 immune mediated clinically significant toxicities and ≥grade 2 immune mediated toxicities, until recovery to grade 1 or resolution**.<br>2) For grade 2 or higher: Also administer corticosteroids followed by a corticosteroid taper<br>3) Treatment can be resumed once prednisone is ≤10mg/day (or equivalent)<br>**document on conmed log* |
| Steroid taper | 1) Inability to reduce corticosteroid dose to prednisone ≤10 mg/day (or equivalent) within 12 weeks | 1) Permanently discontinue. |
| Other adverse reactions that are | 1) life-threatening, severe or grade 3 treatment **related** adverse reactions that **recur,**<br>2) or grade 3 treatment-related toxicity that **does not recover to grade 1 or resolve within 12 weeks (not including alopecia)** | 1 & 2: Permanently discontinue. |
| Thyroid disorder | 1) hyperthyroidism or hypothyroidism | 1) There are no recommended dosage modifications. |
| Infusion reactions | 1) **For Grade 1 symptoms** (mild reaction, infusion interruption not indicated, intervention not indicated): | 1) Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before |

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| | | additional nivolumab and ipilimumab administrations.<br>**document on conmed log* |
| | 2) **Grade 2 symptoms** (moderate reaction requires therapy or infusion interruption but respond promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids], prophylactic medications indicated for < 24 hours) | 2) Stop the nivolumab and or ipilimumab infusion,<br>• begin an IV infusion of normal saline,<br>• treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen)<br>• Corticosteroid or bronchodilator therapy may also be administered as appropriate.<br>• If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve;<br>-if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. -Monitor subject closely.<br>• If symptoms recur then no further nivolumab and or ipilimumab will be administered at that visit.<br>- Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms.<br>**The amount of study drug infused must be |

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| | | recorded on the appropriate page. **The following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administration. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.<br><br>**document all on conmed log* |
| | 3) **Grade 3 or 4 symptoms** (severe reaction, Grade 3 prolonged: [ie not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening, pressor or ventilatory support indicated): | **3)** Immediately discontinue infusion of nivolumab and/or ipilimumab depending on which agent was associated with the reaction.<br><br>• Begin an IV infusion of normal saline and treat the subject as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or |

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| | | diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent) as needed.<br>• Subjects should be monitored until the investigator is comfortable that the symptoms will not recur.<br>• Investigators should follow their institutional guidelines for the treatment of anaphylaxis.<br>• In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).<br>• **Patients who develop a grade 3 or 4 infusion reaction from Ipilimumab may continue adjuvant therapy with Nivolumab at the discretion of the treating physician (must come off Ipilimumab).**<br>• **Patients who develop a grade 3 or 4 infusion reaction from nivolumab to permanently discontinue all protocol treatment.**<br>**document all on conmed log* |

## 5.3 Hepatic Impairment

*Hepatic impairment **prior to** treatment initiation:*

Mild impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any

AST): No dosage adjustment necessary.

Moderate (total bilirubin >1.5 to 3 times ULN (grade 2) and any AST) to severe (total bilirubin >3 times ULN (grade 3 or higher) and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). See required holds above

**5.4 Treatment of Nivolumab and Ipilimumab Related Infusion Reactions**

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions to be reported within 24 hours/1 working day to BrUOG and reported as an SAE if it meets the criteria (as per SAE definitions in section 11). Infusion reactions should be graded according to NCI CTCAE (version 4) guidelines. All infusion reactions, regardless of grade must be reported to BrUOG via AE log and treatment CRF as well.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate, see table above for management and action.

## 6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR *The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on Friday can be used for Monday dosing as this is within 3 days*

| Parameter | Pre-study<br><br>(to be sent to BrUOG prior to registration) | Within 3 days prior to each treatment during Each Cycle of [F] | End of Treatment( defined as post last cycle)(+2 week window provided) | 30 days (+7 days) post last dose of drug | FU[D] |
|---|---|---|---|---|---|
| Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF outside 30 day window | X | | | | |
| Demographics | X | | | | |
| Nivolumab and Ipilimumab nivolumab | | X | | | |
| History [G] | X | | | | |
| Physical examination with performance status | X | X | X | X[I] | |
| Weight | X | X | X | | |
| Vital signs | X | X | X | | |
| Toxicity Assessment | X | X | X | X[H] | X[H] |
| Conmed log | X | X | X | X | |
| CBC, diff, platelet count | X (within 14 days) | X | X | | |
| Na, K, BUN, Cr, AST, ALT, Direct and Total Bilirubin, Albumin | X (within 14 days) | X | X | | |
| Ca, Mg, PO4 | X (within 14 days) | As per institutional standard of care[K] | X | | |
| TSH | X (within 14 days) | As per institutional standard of care[K] | X | | |
| Hep B and C panel (HBsAg, Anti-HBs, Hep B core and HCV RNA and HCV antibody)[L] | X | | | | |
| Serum Pregnancy[E] | X (within 7 days of drug) | | | | |

| | | | | | |
|---|---|---|---|---|---|
| CT scan of<br><br>Chest/abd/pelvis | X[AC](within 12 weeks) | | X[CJ] | | X[DC] |
| CT scan or MRI of brain with contrast | X(within 6 weeks) | | Only if clinically indicated | | Only if clinically indicated |
| EKG[B] | X | | | | |
| Survival and Disease status | | | | X | X[D] |

Cycles are every 6 weeks (+/- 8 days) however, it will not be considered a deviation if a cycle or pre-treatment assessments must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG.

[A]- CT Scan (C/Abd/P) for disease assessment to be performed within 12 weeks of study entry. Report required. (chest X-ray okay with baseline but CT scan should be used during trial).
[B]- EKG within 12 weeks of study entry. Report required
[C]- An MRI or PET scan may substitute for disease assessment.
[D]- Follow-up will be as per institutional standard of care approximately (+/- 2 months) every 6 months for 5 years. Disease status and survival to be sent with follow-up. Imaging of chest/abdomen/pelvis to be done approximately every 6-12 months from last scan, according to institutional practice, with scans to be sent to BrUOG until disease progression. It required that any assessment or pathology showing disease progression be sent to BrUOG
[E] post-menopausal women (surgical menopause or lack or menses $\geq$12 months) do not need to have a pregnancy test, document status. If HCG is not drawn, sites are asked to document menopausal status on lab form.
[F] It is appropriate to use labs from screening for cycle 1 day 1, if labs are within 14 days (pregnancy must be within 7 days as noted above for applicable patients). PS, weight, vitals, AE, conmeds, can be used for cycle 1 day 1 if within 14 days. A physical exam within 7 days prior to cycle 1 day 1 may be utilized. Labs, physical exam, PS, weight, vitals, AEs, conmed log for all subsequent treatments (post cycle 1 day 1) to be within 3 days prior to treatment days. An additional 1 day window is provided for holidays.
[G] Physician note required to be sent.
[H] Adverse event evaluation, inclusive of SAE evaluation, will be done 30 days post last dose of drug (+1 week window). If a patient begins a new treatment, AE evaluation will be stopped unless the patient experiences an event that is thought to be possibly related to the study treatment, SAEs will be captured for 30 days post last dose of drug, regardless if patient begins a new treatment. SAEs occurring outside this 30 day window must be reported if the relationship to either study drug (or the combination) is suspected, even if patient begins a new treatment. It is required to inform BrUOG of patient beginning a new treatment and of surgery/pathology.
[I] Physical to be done in coordination with 30 day toxicity assessment (+ 1 week allowed). Physical post 30 day assessments not required per study
[J]CT scans (or disease assessment by MRI or PET) to be completed after completion of all treatment (if patient stops treatment early then assessment to be done post all treatment)
[K] Any time labs drawn per institutional care, even if not required by study, gradable values must be reported to BrUOG
[L] Patient can be registered with a pending HCV RNA value as long as all other hepatitis results are confirmed non-reactive/negative

## 7.0 ASSESSMENT OF DISEASE PROGRESSION:

Any new biopsy proven cutaneous SCC or basal cell carcinomas, should be excised according to standard guidelines. It is required that BrUOG received pathology and excision information. This will not require patient to be removed from trial.

Any diagnosis of melanoma in-situ will not require patient removal from study but site must submit pathology and excision to BrUOG.

Any diagnosis of melanoma (not in-situ) will be considered recurrence and patient will be required to be removed from study. It is required that all diagnostic information be submitted to BrUOG.

## 8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

**Brown University Oncology Research Group,**
**Brown University**
**Box G-R 001**
**Providence, RI 02912**
**Fax: 401-863-3820**
**Phone: 401-863-3000**
**Email to: bruog@brown.edu**

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites are to be sure that elements to support all inclusion and exclusion criteria are submitted and that all assessments from the schedule of evaluations (section 6) are submitted for registration.

## 9.0 PHARMACEUTICAL INFORMATION

### 9.1 Nivolumab:

Only commercially available nivolumab (OPDIVO) will be utilized. Nivolumab will be stored and administered according to the package insert and institutional standard of care.

Preparation and Administration
Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.
*Preparation*

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

*Storage of Infusion*

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

*Administration*

Administer the infusion over approximately 60 minutes through an intravenous line containing a sterile, non- pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
Do not co-administer other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

*DOSAGE FORMS AND STRENGTHS*

Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

Dosage: Patients who were enrolled and began treatment before Amendment # 2 was IRB approved:
Nivolumab: 3mg/kg q2weeks (+/-3 days) (3 doses per cycle, 12 planned treatments over 6 months total)
Patients enrolled and who start treatment (cycle 1) based on Amendment #2: Nivolumab: 3mg/kg up to a total a total of 240mg IV over approximately 60 minutes (+/- 3 days) (3 doses per cycle, 12 planned treatments over 6 months total)
Doses do not need to be recalculated if weight change is less than 10% of total body weight, as per institutional standard practice.

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Immune Toxicities may include:

- Pulmonary (pneumonitis)
- Gastrointestinal (colitis with diarrhea)
- Endocrinopathies (including inflammation of the thyroid, adrenal and pituitary)
- Hepatic (hepatitis)
- Renal (nephritis)
- Skin (rash)
- Neurological (neuritis)

**9.2 Ipilimumab**

Only commercially available ipilimumab will be utilized.
Ipilimumab will be stored and administered according to the package insert and institutional standard of care.
Brand Names: US

- Yervoy

Pharmacologic Category

- Antineoplastic Agent, Monoclonal Antibody

Dosage Forms: US
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Dosage: Subjects will be treated with 1mg/kg approximately every 6 weeks. Doses do not need to be recalculated if weight change is less than 10% of total body weight, as per institutional standard practice.

Solution, Intravenous [preservative free]:
Yervoy: 50 mg/10 mL (10 mL); 200 mg/40 mL (40 mL) [contains polysorbate 80]
Generic Equivalent Available: US
No Medication Guide and/or Vaccine Information Statement (VIS)
An FDA-approved patient medication guide, which is available with the product information and at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM249168.pdf, must be dispensed with this medication.

**Storage/Stability**
Store intact vials refrigerated at 2°C to 8°C (36°F to 46°C); do not freeze. Protect from light. Prior to preparation, allow vials to sit at room temperature for ~5 minutes. Solutions diluted for infusion are stable for up to 24 hours refrigerated or at room temperature.
Preparation for Administration
Prior to preparation, allow vials to sit at room temperature for ~5 minutes. Inspect vial prior to use; solution may have a pale yellow color or may contain translucent or white amorphous ipilimumab particles; discard if cloudy or discolored. Withdraw appropriate ipilimumab volume and transfer to IV bag, dilute with NS or $D_5W$ to a final concentration between 1-2 mg/mL. Mix by gently inverting, do not shake.
**Compatibility**
Stable in NS, $D_5W$
**Administration**
IV: Infuse over approximately 90 minutes through a low protein-binding in-line filter. Flush per institutional standard volume with NS or $D_5W$ at the end of infusion
**Immune-mediated adverse reactions:**

- Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis,

hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

- Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.
- Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and evaluate clinical chemistries, including liver function tests and thyroid function tests, at baseline and before each dose.

## 10.0 AGENT ACCOUNTABILITY

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug dispensing via institutional practices.

## 11.0 ADVERSE DRUG REACTION (ADR) REPORTING

***BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.***

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Abraxane whether or not considered related to Abraxane. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

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

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

### 11.1 Definitions

**<u>An adverse event</u>** is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

**Serious adverse event (SAE)**

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- a life-threatening adverse drug experience

- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

**Unexpected adverse event**
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

**Life-threatening**
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

**11.2 Monitoring of Adverse Events and Period of Observation**
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

**Abnormal Vital Sign Values**

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event CRF. Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event CRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

### 11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS

Investigators are required by Federal Regulation to report adverse drug reactions. Question regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4. A copy of the CTCAE Version 4 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Serious adverse events occurring more than 30 days after study discontinuation (treatment) need only be reported if a relationship to either study drug (or therapy) or combination of drugs is suspected.

#### 11.3.1 Pregnancies

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug the study drug is to be discontinued immediately. The pregnancy must be reported by the Brown University Oncology Research Group within 24 hours of the Investigator's knowledge of the pregnancy by email and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify BrUOG of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG by facsimile within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to Nivolumab or Ipilimumab must be reported to BrUOG within 24 hours of being made aware of the event via the 3500A. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in

utero exposure to the study drug should also be reported. In the case of a live "normal" birth, BrUOG should be advised as soon as the information is available.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

**11.3.2 Serious Adverse Event Reporting Procedures**

All pregnancies must be reported to the Brown University Oncology Research Group with 24 hours of the Investigator's knowledge.

Non-pregnancy SAE information and all amendments or additions must be recorded on a MedWatch 3500A SAE form and are to be faxed or emailed to BrUOG within 5 business days of being made aware of the event.

Deaths or life threatening events during treatment thought to be related to either drug or combination of the drugs must be reported via Medwatch 3500A to BrUOG within 1 working day of being made aware of the event.

All other deaths during treatment or within 30 days following completion of active protocol therapy (treatment) must be reported within 5 business days or as soon as the investigator is made aware of the event.

Serious adverse events occurring more than 30 days after study discontinuation (treatment) need only be reported if a relationship to either study drug (or therapy) or combination of drugs is suspected.

BrUOG fax: 401-863-3820 Email: bruog@brown.edu

The treating investigator has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, and all sites participating in the trial.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of treatment, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. If the patient begins a new treatment, AE evaluation (not SAE evaluation) will be stopped unless the patient experiences an event that is thought to be possibly related to the study treatment.

**Expedited Reporting by Investigator to BrUOG**

Serious adverse events (SAE) are defined above.
All events must be reported, by FAX or email to the Brown University Oncology Research Group.
The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. **A final report to document resolution of the SAE (defined as discharge from hospital) is required.**

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 business days or as soon as the investigator is made aware of the event. Deaths or life threatening events during treatment thought to be related to either drug or combination of the drugs are to be reported within 1 working day to BrUOG, from the time of being made aware of the event.

**11.4 Assessing Causality:**
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used.

**Yes:** if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

**No:** if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

**11.5 Types of Report:**
**Telephone report**: For SAE's (initial or follow-up) contact BrUOG Central Office at via email within 24 hours upon learning of the event to announce the SAE. Submit notification within 24 hours prior to sending signed written MedWatch 3500A.

**Written report**: Send the copy of the Medwatch 3500A within 5 business days of being made aware of the event to the BrUOG Central Office by email, scan or Fax. Deaths or life threatening events during treatment and thought to be related to either drug or combination of the drugs or pregnancies must be reported via Medwatch 3500A to BrUOG within 1 working day of being made aware of the event. All Grade 3 or 4 infusion reactions that meet SAE criteria are to be reported within 24 hours/1 working day to BrUOG via Medwatch 3500A. All pregnancies must be reported to the Brown University Oncology Research Group within 24 hours of the Investigator's knowledge.

All other deaths during treatment or within 30 days following completion of active protocol therapy (treatment) must be reported within 5 business days or as soon as the investigator is made aware of the event.

Brown University Oncology Research Group
Phone : (401) 863-3000, Fax : (401) 863-3820
Email : BrUOG@brown.edu
**MedWatch 3500A Reporting Guidelines:**
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**

- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to ***each product*** and suspect medication
- Expectedness (based on package insert and ICF) and if event is immune mediated
- Must document BrUOG 324 on 3500A

**Follow-up information:**
A new Medwatch3500A is required to be used for a follow-up, do not add new information to a previously submitted form.

Summarize new information including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report).

All requirements for an initial report remain requirements for a follow-up. It is also required that the report clearly state what new information is being reported at the time of the follow-up.

**11.6 BrUOG Responsibility Regarding Reporting:**
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 7 calendar days after the initial receipt of the signed information via the site submitted MedWatch 3500A. A copy of the form will be kept by the BrUOG Central Office.

**Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to FDA Division fax line that has responsibility for review of IND)**

**Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well**

**11.7 Safety Reporting for IND Holders**
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

**a. Expedited IND Safety Reports:**
**7 Day calendar Telephone or Fax Report:**
The Sponsor-Investigator is required to notify the FDA of any event that is serious, unlisted/unexpected and assessed by the investigator to be possibly related to the use of study drug(s). An unexpected adverse event is one that is not already described in the package insert. All SAEs will be faxed by BrUOG to the FDA as soon as possible but no later than 7 calendar days after BrUOG has received the final signed MedWatch from the site. Each telephone call or fax transmission (see fax number below) should be directed to the MedWatch fax number.

Sites are required to submit MedWatch3500A reports no later than 5 business days after being informed of an event.

**BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA - 0178**

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

## 12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

**Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.**

1. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
2. The physician feels it is in the best interest of the patient to stop the treatment.
3. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
4. Non protocol chemotherapy or immunotherapy is administered during the study
5. Noncompliance with protocol or treatment—major violation
6. Suspected Pregnancy
7. Patient is lost to follow-up
8. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
9. Death

In this event notify:

**Brown University Oncology Research Group (BrUOG) Central Office,**
**Phone: (401) 863-3000**
**Fax: (401) 860-3820**

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for five years with follow-up forms as dictated by the protocol**

## 13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason as well as patients who complete therapy will be followed for five years. At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the last dose of study drug. In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

## 14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Maria Constantinou, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

### 14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

### 14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided by the Brown University Oncology Research Group. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

### 14.3 Protocol amendments or changes in study conduct:

- Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved by Brown University Oncology Research Group, and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group

Examples of amendments requiring such approval

- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

## 15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

**15.1 Good Clinical Practice:** The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

**15.2 Patient Confidentiality:** In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from BrUOG or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

**15.3 Protocol Compliance:** The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from BrUOG and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to BrUOG and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

**15.4 On-site Audits:** Regulatory authorities, the IEC/IRB and/or BrUOG clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who

must provide support at all times for these activities. BrUOG will audit sites based on the BrUOG audit manual and will monitor sites based on the BrUOG SOP.

**15.5 Drug Accountability:** Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's use by each patient will be maintained by the clinical site. Accountability records will include dates, and patient numbers.

**15.6 Premature Closure of the Study:** This study may be prematurely terminated, if in the opinion of the investigator or BrUOG, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

**15.7 Record Retention:**

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Principal Investigator with the assistance of the Brown University Oncology Research Group, as coordinator of this study, are responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (Maria Constantinou, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Amgen will notify the Principal Investigator if an application is filed.

## 16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.

- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

## 17.0 STATISTICS

### 17.1: Toxicity of Adjuvant Ipilimumab and Nivolumab

The primary goal will be to determine the toxicity of adjuvant ipilimumab and nivolumab in patients with melanoma. A rate of 35% or greater grade 3 or grade 4 treatment related non-hematologic toxicities or grade 4 neutropenia or thrombocytopenia, or grade 2 treatment related toxicities that prevent the completion of treatment will be considered to be unacceptable. According to Flemming's method[59] with a maximum overall significance level of 0.05 if there are: 10 or more patients with unacceptable adverse events out of 25 evaluable patients, the study will have exceeded the limit for unacceptable adverse events.

### 17.2 Assessment of disease-free and overall survival

Disease-free and overall survival will be assessed from the day of study entry.

## 18.0 REFERENCES


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APPENDIX A

**Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information**

**BrUOG 324 Adjuvant Nivolumab and Low Dose Ipilimumab for Stage III and Resected Stage IV Melanoma: A Phase II Brown University Oncology Research Group Trial**

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPTIAL NAME> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPTIAL NAME>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

**Nature and Purpose of the Study**

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Maria Constantinou, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to take part in this study because you have malignant melanoma that has spread to lymph nodes or to other parts of your body. While all of the areas involved by the melanoma have been removed by surgery there is a high risk that your cancer will recur (come back).

Treatment options for patients with melanoma at high risk for recurrence include close observation or treatment with drugs that are designed to stimulate the immune system in the hope that it will attack any remaining melanoma cells. These drugs are interferon and ipilimumab. While ipilimumab has been shown to reduce the risk of melanoma recurring, at the dose used in the study that showed it to be effective this drug has serious and sometimes life-threatening side effects. In this study we are testing a lower dose of ipilimumab. Your doctor will explain these options and the side effects of these options.

In patients with advanced melanoma, where the cancer has spread to other areas of the body and cannot be removed with surgery, the combination of Ipilimumab with another drug that stimulates the immune system, Nivolumab has been shown to be both more effective at shrinking melanoma tumors and preventing them from growing and to have fewer serious side effects than high dose Ipilimumab by itself.

Your doctors are studying how well the combination of lower dose Ipilimumab and Nivolumab are tolerated and how effective this combination is in preventing melanoma from coming back in patients like

you. While Nivolumab is FDA approved to treat patients with advanced melanoma, it is not FDA approved to treat patients like you who are at high risk for their melanoma to recur. In this study you will receive the FDA approved dose of Nivolumab for advanced melanoma together with one-third of the standard dose of Ipilimumab, and the Ipilimumab will be given approximately once every 6 weeks instead of every 3 weeks. The investigational aspect of the trial is the use of Nivolumab and lower dose Ipilimumab to try to prevent recurrence of melanoma after surgery.

**How Many People will take part in the Study?**

Approximately 25 patients will participate

**Explanation of Procedures**

**What will happen if I take part in this research study?**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests, while on the study. They are part of regular cancer care.

- Medical history prior to starting treatment.
- Physical examination with performance status and toxicity assessment, weight and vitals prior to starting
- Blood tests prior to starting treatment (approximately 3 tablespoons of blood). If you are a female of childbearing age you will also have a pregnancy test within 7 days of study treatment
- CT scan, PET scan, or MRI of the chest, abdomen and pelvis, and a CT or MRI of the brain, prior to starting treatment
- EKG prior to starting treatment

**While on study:**

You will receive nivolumab by vein (IV) over 60 minutes, approximately every 2 weeks for 12 treatments. You will also receive Ipilimumab IV over 90 minutes approximately every 6 weeks for 4 treatments. The two drugs will be given together at the start of each 6 week cycle, then the nivolumab will be given by itself approximately 2 weeks and 4 weeks later. You will be receiving nivolumab and ipilimumab for about 6 months.

You will have the following completed while on study treatment. These assessments are considered a part of regular cancer care.

- Physical examination with performance status and toxicity assessment, review of medication list, weight and vitals approximately every 2 weeks while on treatment
- Blood tests (approximately 3 tablespoons of blood) approximately every 2 weeks while on treatment
- CT scan, PET scan, or MRI of the chest, abdomen and pelvis at treatment completion. MRI or CT of the brain will be performed if clinically indicated by your treating physician

**End of study treatment** (6-7 months, unless the study treatment has to be stopped early for some reason):

- Physical examination, with performance status and toxicity assessment (at the end of treatment and again 30 days post the last dose of drug)
- Blood tests (approximately 3 tablespoons of blood) and at the end of treatment and 30 days post last dose of drug
- CT scan of the chest, abdomen and pelvis
- CT or Brain MRI as needed

**Follow-up:**

- CT scan of the chest, abdomen and pelvis approximately every 6-12 months (your doctor may decide to do these more frequently) for up to 5 years or until the melanoma recurs (returns or gets worse)
- CT or Brain MRI at the discretion of your doctor

After completion of treatment you will be seen by your doctor approximately every 6 months for 5 years so that he/she can document if your melanoma has recurred and that you are still alive.

**Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

**Costs for participating in this study**

All the services you will receive during this research study are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. These include all study doctor visits, blood tests, Nivolumab and Ipilimumab drugs and administration costs, drugs used to reduce side effects, CT scans, MRIs, PET scans and EKGs. Therefore, all of the services listed in this paragraph will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance or your insurance does not cover these services, you will be responsible for those costs.

**Contact Information:** If you have any questions regarding this study, you may contact your site's Principal Investigator, <INSERT NAME AND CONTACT>

**Discomforts and Risks**

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. Taking part in this study may lead to time away from work.
**Nivolumab and Ipilimumab are both immunotherapy drugs. The anticipated side effects of each of the drugs, at the doses used in this study, are approximately the same. There are also some side effects which may not yet be known.**

**Possible Side Effects of Ipilimumab**

Ipilimumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells from white blood cells). Immune-mediated side effects have been reported in patients receiving ipilimumab. In clinical trials, most side effects were reversible and managed by stopping ipilimumab temporarily, administration of supportive care. While rare, immune mediated side effects may also occur after stopping ipilimumab. These are considered late onset immune mediated toxicities, which may begin even months after stopping treatment. Your doctor will closely monitor you after you stop treatment and provide supportive care as necessary.

**Common (>20%)**

- Diarrhea, nausea
- Tiredness
- Rash which may cause fever and swollen, red, painful bumps in the skin

**Occasional, some may be serious (<20%-4%)**

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Constipation, vomiting
- Swelling of the body which may cause shortness of breath
- Difficulty swallowing, eating
- Chills, fever
- Reaction during or following infusion of the drug
- Damage to organs leading to prolonged hospitalization *(The agent can induce immune reactions and inflammation which can cause serious and life-threatening damage to organs including the skin, colon, gut, liver, pancreas, heart, brain, muscle, kidney, and endocrine glands)*
- Loss of appetite, dehydration
- Abnormal movement of the facial muscles

- Headache
- Weakness and paralysis
- Kidney damage which may require dialysis
- Itching, hives
- Low blood pressure which may cause feeling faint

**Rare and serious (< 3% or fewer)**

- Bleeding
- A tear or hole in the stomach that may require surgery
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body.
- Pericardial effusion
- Adrenal insufficiency (adrenal glands do not produce enough cortisol hormone)
- Hypophysitis (inflammation of pituitary gland)
- Confusion
- Dizziness

**Possible Side Effects of Nivolumab**

Nivolumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving Nivolumab. In clinical trials, most side effects were reversible and managed by stopping Nivolumab temporarily, administration of corticosteroids and supportive care. While rare, immune mediated side effects may also occur after stopping Nivolumab. These are considered late onset immune mediated toxicities, which may begin even months after stopping treatment. Your doctor will closely monitor you after you stop treatment and provide supportive care as necessary.

**Common (>20%)**

- Tiredness

**Occasional, some may be serious (<20%-4%)**

- Anemia which may require blood transfusion
- Swelling and redness of the eye which may cause blurred vision with a chance of blindness
- Pain
- Constipation, diarrhea, nausea, vomiting
- Dry mouth
- Fever
- Loss of appetite
- Cough, shortness of breath

- Swelling of the body, including the brain, which may cause shortness of breath, headache, tiredness, and nerve pain
- Itching, rash

**Rare and serious (<3% or fewer)**

- Visual disturbances
- A tear or hole in the stomach that may require surgery
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Damage to the body by own immune system
- Weakness and paralysis
- A condition with high blood sugar which may cause tiredness, frequent urination, excessive thirst, headache, nausea, vomiting, and can result in coma
- Muscle weakness
- Kidney damage which may require dialysis
- Pericardial effusion
- Edema (including periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema)
- Pleural effusion
- Adrenal insufficiency (adrenal glands do not produce enough cortisol hormone)
- Hypophysitis (inflammation of pituitary gland)
- Dehydration
- Confusion
- Dizziness

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

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

**Please inform your study doctor or nurse AT ONCE if you experience any of the following:**

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;

- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

**Reproductive Risks From nivolumab and ipilimumab**

Nivolumab and ipilimumab may decrease sperm count. This is usually temporary but can be permanent, which would result in sterility (not being able to father a baby).

Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study.

If you are a woman or man of childbearing potential you must practice an effective method of birth control while receiving study treatment and for at least 2 months after completing or discontinuing study treatment. Ask your study doctor for more information regarding preventing pregnancy during the study treatments.

You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

**Antiemetics (anti-nausea medications):** Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.
You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

**Venipuncture** (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.
When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.
In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

**Risk of CT imaging:** CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist. There is no significant risk from this amount of radiation.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

## Benefits

While your doctor hopes that ipilimumab and nivolumab will lower the risk that your melanoma will come back, and the side effects of this combination are not too severe, this is not yet known. We do know that the information from this study will help doctors learn more about these drugs as a treatment for cancer. This information could help future cancer patients.

## Alternative Therapies

What other choices do I have if I do not take part in this study?

- Treatment with standard (higher) dose ipilimumab
- Treatment with high dose interferon
- Taking part in another study
- Being followed closely for recurrence of melanoma by CT or other scans and not receiving treatment.

Talk to your doctor about your choices before you decide if you will take part in this study.

## Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your

health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

**Medical Treatment/Payment in Case of Injury**

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Maria Constantinou nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

**Rights and Complaints**

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <INSERT CONTACT NAME OF IRB>

**Confidentiality**

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

 The researcher and their support staff;
 The study sponsor: Dr. Maria Constantinou and central coordinating office: The Brown University Oncology Research Group and its representatives
 Doctors, nurses, laboratories and others who provide services to you in connection with this study;
 The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
 The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
 People who volunteer to be patient advocates or research volunteer protectors;
 Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.
You have the right to refuse to sign this form and not participate in the research. Your refusal would have no effect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.
If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONATACT INFORMATION>
For more detail about your privacy rights see the <INSERT HOSPITAL NAME> which has or will be given to you.

**Research authorization for use and disclosure of information.**

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to Maria Constantinou, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONTACT>

**Uses and releases covered by this authorization (permission)**

**Who will release, receive, and/or use your information?** This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

☒ Every research site for this study, including this hospital, and including each site's research staff and medical staff

☒ Health care providers who provide services to you in connection with this study

☒ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol

☒ The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: The Principal Investigator Maria Constantinou, MD and BrUOG, the central coordinating group for the study, and their representatives

☒ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights
☒ The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
☒ Principal Investigator and other Investigators
☒ Study Coordinator
☒ Additional members of the Research Team
☐ The Patient Advocate or Research Volunteer Protector: _____
☒ Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
☐ Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
☒ Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee
☐ The members and staff of the hospitals affiliated Privacy Board (if such a board is used)

☐ Others: _____
* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☒ The entire research record and any medical records held by the hospital may be used and released.
☐ The following information: _____

**SIGNATURE**

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

**This informed consent document expires on _____.**

**DO NOT sign this document after this expiration date**

**The Researcher is required to provide a copy of this consent to you.**

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____

Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____

Signature of Translator Date

_____ _____ _____

Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

APPENDIX B: Checklist

Adjuvant Nivolumab and Low Dose Ipilimumab for Stage III and
Resected Stage IV Melanoma:
A Phase II Brown University Oncology Research Group Trial

**Inclusion Criteria**

_____(y/n) Pathologically or cytologically proven melanoma. The primary site of melanoma may be cutaneous or other body site such as ocular or anorectal. Document in writing location of cutaneous

_____(y/n) Completely resected stage III (lymph node positive) or resected stage IV disease. Patients with stage T4BN0 are also eligible. All patients must be disease free to be eligible. Confirmation to be sent to BrUOG.

_____(y/n) It is required that patients with stage IIIA disease have > 1mm nodal involvement via pathology assessment of the resected node.

_____(y/n) No prior treatment for melanoma other than surgical resection or radiation.
_____(y/n) At least 4 weeks since prior major surgery and 3 weeks since radiation from time of registration. Submit on prior treatment CRF.

_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥18
_____(y/n) ECOG PS 0-1

_____(y/n) Must be willing to consent to use effective contraception while on treatment and for 2 months after the end of treatment.

_____(y/n) CT scan of the chest/abdomen/pelvis within 12 weeks of study entry. Patients can have PET/MRI of the chest/abdomen/pelvis instead. Chest Xray okay baseline.

_____(y/n) MRI or CT brain with contrast within 6 weeks of study entry

_____(y/n) EKG within 12 weeks study entry

_____(y/n) Absolute neutrophil count ≥ 1,500/ul, Date_____ Value: _____

_____(y/n) Platelet ≥ 100,000/uL, Date_____Value : _____

_____(y/n) HGB >/= 9.5 g/dL Date_____Value : _____

_____(y/n) Total bilirubin ≤ 1.5 x ULN except subjects with normal direct bilirubin or those with known Gilbert's syndrome, Date_____ Value : _____ Send information to BrUOG if patient has known Gilbert's syndrome

_____(y/n) AST and ALT ≤ 2.5x ULN

_____(y/n) Albumin ≥ 2.5g/dL

_____(y/n) Creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 50ml/min

_____(y/n) Women of child bearing potential must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to Day 1 of treatment. Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, please document status.

**Exclusion Criteria**:

_____(y/n) Patients with an active, known or suspected autoimmune disease. Subjects with vitiligo, controlled type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

_____(y/n) Prior treatment with an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody

_____(y/n) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

_____(y/n) Known history of HIV or known acquired immunodeficiency syndrome

_____(y/n) positive test result (chronic or acute) hepatitis B or C

_____(y/n) Clinically significant coagulopathy. Therapeutic use of anticoagulants are allowed (put on conmed log).

_____(y/n) Patients with unstable angina (anginal symptoms at rest) or new-onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.

_____(y/n) History of autologous transplant or organ allograft even if not taking immunosuppressive medications

_____(y/n) Pregnant or lactating or breastfeeding- see 3.2.3.

_____(y/n) Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) or investigational anti-cancer drug

_____(y/n) Unwillingness or inability to follow the procedures required in the protocol, to document

_____(y/n) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

_____(y/n) Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast. Documentation required to be sent to BrUOG

_____(y/n) History of severe hypersensitivity reaction to any monoclonal antibody to confirm in writing.

_____(y/n) Brain Metastases (whether resected or not)

_____(y/n) Leptomeningeal disease

_____(y/n) Bone metastases

Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed ___ Not Applicable _

2) Heme/Onc initial note Enclosed __Not Enclosed ___ Not Applicable _

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed ____ Not Applicable __

6) ICF signature page

7) Other documentation

It is required that each item from section 6 be submitted to BrUOG along with confirmation via source to match each inclusion and confirm each exclusion criteria.

IRB approval date of protocol: _____

Date of treatment _____

Hospital where patient will be treated with Oncologist: _____

Name of treating physician: _____

Your signature: _____

**APPENDIX C**

ECOG PATIENT PERFORMANCE STATUS

| STATUS | KARNOFSKY | ZUBROD-ECOG-WHO | Description |
|---|---|---|---|
| No complaints | 100 | 0 | Normal activity |
| Able to carry on normal activities | 90 | 1 | Symptoms, but fully ambulatory |
| Normal activity with effort | 80 | | |
| Cares for self. Unable to carry on normal activity or to do active work | 70 | 2 | Symptomatic, but in bed <50% of the day |
| Requires occasional assistance, but able to care for most of his needs | 60 | | |
| Requires considerable assistance and frequent medical care | 50 | 3 | Needs to be in bed >50% of the day, but not bedridden |
| Disabled, requires special care and assistance | 40 | | |

| | | | |
|---|---|---|---|
| Severely disabled. Hospitalization indicated though death non imminent | 30 | 4 | Unable to get out of bed |
| Very sick. Hospitalization<br><br>Necessary. Active support treatment necessary | 20 | | |
| Moribund | 10 | | |
| Dead | 0 | | |

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

**APPENDIX D**

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms