

**Nivolumab and Ablation For Patients With Advanced Non-Small Cell Lung Cancer  
Progressing After at Least One Prior Therapy For Metastatic Disease:  
A Brown University Oncology Research Group Phase II Study**

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## TABLE OF CONTENTS

<u>Section</u>	<u>Page</u>
1.0 OBJECTIVES	3
2.0 BACKGROUND	3
3.0 PATIENT ELIGIBILITY	5
4.0 TREATMENT	6
5.0 TOXICITIES, ASSESSMENT, AND DOSE MODIFICATIONS	7
6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR	11
7.0 RESPONSE ASSESSMENT	14
8.0 PATIENT REGISTRATION	16
9.0 PHARMACEUTICAL INFORMATION	17
10.0 AGENT ACCOUNTABILITY	18
11.0 ADVERSE DRUG REACTION REPORTING	18
12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY	23
13.0 FOLLOW UP	24
14.0 REGULATORY CONSIDERATIONS	24
15.0 DATA MONITORING/QUALITY ASSURANCE/ RECORD RETENTION	25
16.0 DATA SAFETY AND MONITORING BOARDS	26
17.0 STATISTICAL CONSIDERATIONS	27
18.0 REFERENCES	28

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### APPENDIX SECTION:

APPENDIX A INFORMED CONSENT

APPENDIX B ELIGIBILITY CHECKLIST

APPENDIX C ADVERSE DRUG REACTION MEMORANDUM

APPENDIX D COMMON TOXICITY CRITERIA

APPENDIX E ECOG PERFORMANCE STATUS

APPENDIX F CASE REPORT FORMS

## **1.0 OBJECTIVES**

### **1.1 Primary Objective**

1.1.1. To evaluate the response rate of the combination of ablation and the PD-1 inhibitor nivolumab for patients with non-small cell lung cancer (NSCLC) who have progressed following at least 1 prior chemotherapy regimen for metastatic or locally advanced disease.

### **1.2 Secondary Objectives**

1.2.1 To evaluate the disease-free and overall survival for the combination of ablation and the PD-1 inhibitor nivolumab for patients with NSCLC who have progressed following at least 1 prior chemotherapy regimen for metastatic or locally advanced disease.

1.2.2 To evaluate whether ablation increases tumor PD-L1 expression.

## **2.0 BACKGROUND:**

**Lung Cancer:** Lung cancer is the most common cause of cancer death. Worldwide, in 2012 there were approximately 1.8 million new cases of lung cancer and an estimated 1.6 million deaths.<sup>1</sup> In the United States, there will be an estimated 224,000 new cases of lung cancer and 159,000 deaths in 2014.<sup>2</sup>

**Chemotherapy for Metastatic NSCLC:** First-line treatment for patients with advanced NSCLC without an EGFR or ALK mutation is combination chemotherapy generally including a platinum compound.<sup>3,4,5</sup> Second-line chemotherapy often utilizes a single chemotherapy drug not utilized in the first-line regimen such as pemetrexed or docetaxel.<sup>6,7</sup> Response rates to second line treatment are about 10%. The average survival for patients with metastatic NSLCC with multiple lines of chemotherapy is about 1 year.<sup>3-7</sup>

**PD-1/PD-L1 Inhibition:** Stimulating the immune system to fight lung cancer represents one of the most remarkable clinical achievements in the last decade in thoracic oncology.<sup>8</sup> Programmed death ligand 1 (PD-L1) is a transmembrane protein that was first identified for its role in the maintenance of self-tolerance and prevention of autoimmunity.<sup>9</sup> Engagement of PD-L1 on dendritic cells with the programmed death 1 (PD-1) receptor on T cells delivers an inhibitory signal that promotes T cell anergy or apoptosis.<sup>10</sup> This immunoinhibitory checkpoint is often subverted by tumor cells that over-express PD-L1 in order to escape immunosurveillance in the tumor microenvironment. There is a strong correlation between PD-L1 expression and prognosis in cancer. Blockade of the interaction between PD-L1 on tumor cells and PD-1 on T cells with anti PD-1/anti PD-L1 antibodies reverse T cell suppression within tumors, thereby promoting effective anti-tumor immune responses.<sup>11</sup>

**Nivolumab in NSCLC:** Nivolumab is a fully human IgG4 PD-1 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response.

Patients with advanced NSCLC who had been previously treated with a prior platinum-containing regimen received nivolumab at a dose of 1, 3, and 10 mg/kg.<sup>12,13</sup> The maximum-tolerated dose was not reached in this trial, and all doses were found to be safe. In the initial phase expanded phase I study reported in the New England Journal of Medicine (NEJM) a total of 122 patients with NSCLC were enrolled.<sup>12</sup> The majority of patients with NSCLC were heavily pretreated; 55% of patients received 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. Disease response was seen in squamous as well as non-squamous histology (six of 18 patients [RR, 33%] with squamous histology and seven of 56 patients [RR, 12%] with non-squamous histology). Nivolumab has been well tolerated. Only 8% of the patients with NSCLC experienced grade 3 or 4 treatment-related AEs. The most common grade 3 and 4 treatment-related AEs in patients with NSCLC were fatigue, elevated AST, and pneumonitis. Nine patients (3%) of the total trial population developed pneumonitis.

Tumor PD-L1 expression appeared to be associated with response. Among the first 76 assessable patients with NSCLC without tumor expression of PD-L1 there were no documented tumor responses, but 36% of patients with tumor PD-L1 expression were objective responders in the NEJM article.<sup>12,13</sup> However, the FDA granted approval of nivolumab in all patients with squamous cell NSCLC regardless of PD-L1 expression based on complete data of the entire 122 patients with NSCLC in the expanded phase I as well as subsequent BMS trials with nivolumab. Similarly, data with the Merck PD-1 antibody MK-3475, suggests that while activity in NSCLC is higher in tumors with PD-L1 expression, benefit appears to be present even in tumors without expression.<sup>14</sup> In KEYNOTE-001 evaluating MK-3475, using the 50% cutoff point for PD-L1 expression, about 25% of patients with NSCLC were strongly positive for PD-L1 expression. The overall response rate to MK-3475 for both PD-L1–positive and –negative groups was 19%. Median progression-free survival was 14.1 weeks in the PD-L1–positive patients vs 9.3 weeks in the weakly positive (1%–49% cutoff) and negative patients. Overall survival was 9.3 vs 7.3 months, respectively, following MK-3475 in patients with NSCLC, which was not statistically significant between the groups.

Given the unprecedented response seen in heavily pretreated patients with NSCLC, the following phase III studies were initiated:

- Nivolumab Compared to Docetaxel in Previously Treated Metastatic Non-squamous NSCLC (CheckMate 057) NCT01673867.
- Nivolumab Compared to Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC) (CheckMate 017) NCT01642004
- Nivolumab Versus Investigator's Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer (CheckMate 026) NCT02041533

On March 4<sup>th</sup>, 2015 Nivolumab received FDA approval to treat metastatic squamous cell lung cancer with progression on or after first-line chemotherapy based on results from Check Mate 057. Nivolumab's efficacy to treat squamous NSCLC was established in this randomized trial of 272 participants, of whom 135 received Nivolumab and 137 received docetaxel. The trial was designed to measure the effect on overall survival. Participants who received Nivolumab lived 3.2 months longer than those participants who received docetaxel.

At the annual meeting of the American Society of Clinical Oncology, May 30, 2015, the results of Checkmate 057 were released. A survival benefit of nivolumab as compared to docetaxel was demonstrated for patients with metastatic non-squamous cell lung cancer. The 12 month overall survival was 51% for nivolumab compared with 39% for docetaxel. The response rate was 19% for nivolumab versus 6% for docetaxel. Grade 3/4 toxicities were higher with docetaxel (20% versus 7%). Patients with tumors with PD-L1 expression had significant benefit with nivolumab as compared to docetaxel while tumors without PD-L1 expression had similar outcomes.

**Ablation as a Treatment For Cancer:** Ablation is a local modality that involves placing a needle or electrode under radiologic guidance into the center of a tumor and using heat or cold to

destroy a defined area.<sup>15</sup> Dupuy et al has demonstrated that ablation is an important treatment for lung cancer.<sup>16-18</sup> Radiofrequency ablation (RFA) emits a high frequency alternating current from the tip of an electrode into the tissue surrounding that electrode.<sup>19</sup> As the ions within the tissue attempt to follow the change in the direction of the alternating current, their movement results in frictional heating of the tissue. As the temperature within the tissue becomes elevated beyond 60°C, cells begin to die, resulting in a region of necrosis surrounding the electrode.<sup>19</sup> Ablation can be used both to kill tumor cells but also to relieve pain. Dupuy et al pioneered ablation to reduce pain from bone metastases and this currently is an FDA indication.<sup>20</sup>

Cryoablation uses cold injury to kill tumors.<sup>21</sup> This procedure uses liquefied gases such as argon that cool as they expand. This freezing process, unlike other ablative techniques, is unique in maintaining intact intracytoplasmic organelles and the cell ultrastructure, while opening up the plasma membrane to immune cell exposure thus inducing higher post-ablative immunogenicity.<sup>21</sup> These intact tumor antigens are captured by dendritic cells and macrophages, thereby mounting a local and systemic immune response involving IL-1, IL-6 and nuclear factor- $\kappa$ B (NF- $\kappa$ B)-dependent cytokines such as TNF $\alpha$ .<sup>23-25</sup> Histological studies have shown post-cryoablation tumor infiltrates of neutrophils, followed by substantial macrophage recruitment; ELISA studies have shown systemic elevation of tumor-specific antibodies, NK cell activity, increased tumor-specific T cell response in regional lymph nodes and the level of systemic circulating T cells.<sup>26, 27</sup> ***Therefore, since cryoablation enhances the immunogenicity of tumors, the combination of cryoablation and nivolumab may be synergistic.***

Recent data from Sloan Kettering suggests that thermal ablation may also activate the immune system. Serum interleukin-6 (IL-6) increases after thermal ablation. IL-6 is released by several cell types including type-2 helper T-cells (Th2), and plays a role in type-1 helper T-cells (Th1) and Th2 differentiation.<sup>28</sup> Furthermore; heat-based ablation increases the proportions of circulating Th1 and CTLs more than cryoablation. Heat-based ablation therefore is another approach to enhance systemic anti-tumor immunity by increasing CTL levels and optimizing Th1/Th2 balance.<sup>29</sup>

**Protocol Rationale:** Nivolumab releases the inhibition of the immune system against human cancers. Dramatic and sustained activity has been observed in advanced lung cancer. Ablation may stimulate the immune system by exposing new tumor antigens. Since tumors that express PD-L1 may be more likely to respond to nivolumab, if ablation increases PD-L1 expression (which has not been studied) this treatment may enhance the activity of nivolumab at both the treated site and in other, non-treated, tumors. Ablation is already an FDA approved treatment for cancer. Nivolumab was recently FDA approved for second line treatment of advanced squamous cell NSCLC. The goal of the study will be to determine if the combination of nivolumab and ablation has higher systemic activity than previously reported with nivolumab alone.

### **3.0 ELIGIBILITY:**

#### **3.1 Inclusion Criteria:**

3.1.1 Pathologically or cytologically confirmed NSCLC

3.1.2 Stage IIIB or stage IV.

3.1.3 Patient to meet either criterion A or B:

A) Patient must have progressed after at least 1 line of systemic treatment (IV or oral) for metastatic or locally advanced disease. Must provide documentation systemic treatment was for either locally advanced or metastatic. Must also provide scan or assessment to show most recent progression, pre-enrollment certifying progression of disease to meet inclusion eligibility of progression. Radiation does not count as 1 line.

FDA exemption 6/30/15, 6/30/15, 8/17/15 (for LOCR initial), Amendment #1 10/5/15 v 2 HS approval, Amendment # 2 11/9/15, Amendment #3 3/4/16, Amendment # 4 4/7/16, Amendment # 5 6/1/16 V2, Amendment # 6 7/7/16, Amendment # 7 11/16/16, Amendment # 8 2/22/17, Amendment #9 5/22/17

B) Patients progressing within 6 months of completion of neoadjuvant or adjuvant chemotherapy are also eligible without having treatment for metastatic disease (for example patient with stage I disease undergoes resection, receives systemic chemotherapy and then progresses to the liver (now stage IV) within 6 months of chemotherapy). Radiation does not count as 1 line.

3.1.4 Ablation for advanced lung cancer is being considered by the treating physician for treatment or prevention of symptoms such as pain, bleeding or obstruction- Documentation is required in writing by MD for this criterion.

3.1.5 At least 1 site of measurable disease that will not be treated with ablation. Sites to send confirmation on which lesion of measurable disease will not be ablated for tracking of response.

3.1.6 At least 3 weeks since prior systemic treatment and/or radiation therapy for patient's NSCLC (from treatment day 1 on study)

3.1.7. No brain metastases except for patients whose metastases have been removed by surgical resection or have had stereotactic radiation or gamma knife with no evidence of active disease on MRI within 28 days of starting treatment.

3.1.8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2.

3.1.9. Life expectancy of at least 12 weeks.

3.1.10. Required entry laboratory parameters within 14 days of study entry: Granulocytes  $\geq$  1000/ $\mu$ l; platelet count  $\geq$ 75,000/ $\mu$ l; Creatinine  $\leq$  1.5x upper limit normal mg/dl; Bilirubin  $<$  1.5x upper limit normal; AST  $\leq$  3 x upper limit of normal.

3.1.11. Age  $>$  18 years

3.1.12. 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 up to 2 months after.

3.1.13. Written informed consent.

### **3.2 Exclusion Criteria:**

3.2.1 Patients with a history of clinically significant chronic autoimmune disease

3.2.2. Prior therapy with antibodies that modulate T-cell function defined as: anti-CTLA-4, anti-PD-1, and anti-PD-L1 drugs.

3.2.3. Conditions currently requiring immunosuppressive medications

3.2.4. Known history of HIV or hepatitis B or C

3.2.5. Bleeding diathesis or coagulopathy that in the investigators opinion would prevent ablation from being safely performed.

3.2.6. 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.

3.2.7. History of organ allograft even if not taking immunosuppressive medications

3.2.8. Pregnant or breast-feeding.

**3.3 Re-screening:** If a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

## **4.0 TREATMENT:**

**4.1 Nivolumab:** 3mg/kg up to a maximum dose of 240mg IV over approximately 60 minutes on Day 1 +/- 3 days every 2 weeks until progression for a maximum of 2 years.

It will also not be considered a deviation if a cycle or pre-cycle assessment must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG. While efforts should be made to have cycles be every 2 weeks (+/- 3 days), further allowances are allowed as long as cycles are not < 10 days.

**4.2 Ablation:** Either cryoablation or thermal ablation may be performed as per standard institutional policies. Ablation should be performed within 1 week (7 days) of the initial treatment with nivolumab, to occur within the first cycle (14 days) of treatment. Additional ablation procedures may be performed as clinically indicated such as for pain control including the treatment or prevention of pain or obstruction or as per institutional standard of care. There must be a minimum of 60 days between each ablation (60-90 days is preferable). Standard institutional procedures may be used in ablation. One or more than one lesion may undergo ablation as per investigator judgement and institutional standard of care. At least one measurable site of disease cannot be ablated so that it may be followed for response. This location should be chosen at baseline with enrollment-see section 3.1.5

During the same procedural period as ablation, if patient has consented and agreed, a tumor tissue biopsy may be obtained prior to each ablation, as per institutional standard of care. This biopsy may be assessed for future correlative studies such as assessment of PD-L1 by immunohistochemical staining and will allow for correlation to response.

The following treatments must not be administered during the study: Immunotherapy other than the study drug, immunosuppressive drugs [i.e., chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions or for the treatment of immune related adverse events (irAEs)}, or other experimental pharmaceutical products. Short term administration of systemic steroid (i.e., for allergic reactions or the management of irAEs is allowed).

Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion.

#### **Requirements For Ablation:**

Pre-ablation labs will be done within 2 weeks of ablation (prior to). If the counts are done early and would preclude the patient from ablation, labs should be repeated on the day of the procedure prior to cancelling.

Ablation cannot occur unless the following criteria are met:

PLT  $\geq 50 \times 10^9/L$  (50,000/mm<sup>3</sup>)  
INR <1.8

#### **5.0 DOSE MODIFICATIONS OF NIVOLUMAB AND TOXICITY MANAGEMENT:**

Adverse events will be graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4

## **5.1 Nivolumab Dose Modifications:**

No dose reductions of nivolumab are included in the study. Any adverse event, laboratory abnormalities, or undercurrent illness which in the judgment of the investigator, can warrant delaying the dose of study medication.

## **5.2 The following must be confirmed prior to dosing a patient with Nivolumab:**

- 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.

## **5.3 Hold treatment until recovery to grade 1 or resolution for:**

- 1) If AST or ALT >3 to 5 times ULN (grade 2) or total bilirubin >1.5 to 3 times ULN (grade 2): **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).

\*\*for possibly, probably or definitely related to nivolumab see section 5.3, 2.I below

\*\*AST or ALT >5 times ULN (grade 3) or total bilirubin >3 times ULN (grade 3) or severe/life-threatening immune-mediated hepatitis: **Permanently discontinue**. \*\*see section 5.3 (this section), 2\*\* below

- 2) Immune-mediated hepatitis:

- I. Grade 2 or higher transaminase elevations that are possibly, probably or definitely related to nivolumab (with or without total bilirubin elevations): Withhold treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

\*\* Severe (grade 3) or life-threatening (grade 4) transaminase elevations: Permanently discontinue treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

- 3) **Colitis:**

- I.** Grade 2 (duration >5 days): 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
- II.** Grade 3: Also administer systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

- 4) **Pneumonitis:** Pneumonitis (grade 2); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper

- 5) **Other immune-mediated toxicities:** Other immune-mediated toxicities; also administer high-dose systemic corticosteroids followed by a corticosteroid taper (over 1 month)

- 6) **Creatinine** >1.5 to 6 times ULN (grade 2 or 3) or >1.5 times baseline (grade 1): 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).

#### 5.4 Discontinue treatment (remove patient from study), for following:

- 1) AST or ALT >5 times ULN (grade 3) or total bilirubin >3 times ULN (grade 3) or severe/life-threatening immune-mediated hepatitis: **Permanently discontinue.**
- 2) Colitis
  - I. Colitis: (grade 4); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper
  - II. Colitis (recurrent)
- 3) Pneumonitis  
Pneumonitis (grade 3 or 4); also administer high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent) followed by a corticosteroid taper
- 4) Inability to reduce corticosteroid dose to prednisone  $\leq$ 10 mg/day (or equivalent) within 12 weeks.
- 5) Other adverse reactions that are life-threatening, severe or grade 3 treatment related adverse reactions that recur, or persistent grade 3 treatment-related toxicity that does not recover to grade 1 or resolve within 12 weeks (except alopecia)..
- 6) Creatinine >6 times ULN (grade 4): Permanently discontinue; initiate high-dose systemic corticosteroids
- 7) Severe (grade 3) or life-threatening (grade 4) transaminase elevations: Permanently discontinue treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

#### 5.5 Hepatic Impairment

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

Mild impairment (total bilirubin  $\leq$  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 and any AST) to severe (total bilirubin >3 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

##### *Hepatotoxicity during treatment:*

AST or ALT >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN: 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) .

AST or ALT >5 times ULN or total bilirubin >3 times ULN or severe/life-threatening immune-mediated hepatitis: Permanently discontinue.

Immune-mediated hepatitis:

Grade 2 or higher transaminase elevations (with or without total bilirubin elevations): Withhold treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

Severe (grade 3) or life-threatening (grade 4) transaminase elevations: Permanently discontinue

treatment and initiate high-dose systemic corticosteroids (prednisone 1 to 2 mg/kg daily or equivalent)

## **5.6 Thyroid Disorders**

Thyroid disorder (hyperthyroidism or hypothyroidism): There are no recommended dosage modifications.

## **5.7 Treatment of Nivolumab Related Infusion Reactions**

Since nivolumab contains 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 should be reported within 24 hours to BrUOG and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (version 4) guidelines.

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

**For Grade 1 symptoms** (mild reaction, infusion interruption not indicated, intervention not indicated): Remain at bedside and monitor 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 additional nivolumab administrations.

**For 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) Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be 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.

**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): Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV

administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent) as needed. Subjects should be monitored until the investigator is comfortable that the symptoms will not recur. **Nivolumab will be permanently discontinued.**

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subjects until recovery from symptoms. 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).

#### 6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study (to be sent to BrUOG prior to registration)	Within 3 days prior to Day 1 of Each Cycle of Nivolumab (approximately every 2 weeks) <sup>F</sup>	While on Nivolumab therapy (Every 12 weeks approximately every 6 cycles)	Ablation <sup>L</sup> Cycles 1(1 week after starting drug) and prior to each additional ablation (if performed)	End of Treatment (2 week window provided)	30 days post last dose of drug	FU <sup>D</sup>
Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X						
Demographics	X						
Conmed log <sup>P</sup>	X	X	X	X	X		
Nivolumab <sup>K</sup>		X					
Optional labs: 3, 6ml purple top tubes to Dr. Loren Fast at RIH at multiple time points	X	X <sup>O</sup>		X <sup>O</sup>			X <sup>O</sup>
Optional Tissue biopsy				X <sup>M</sup>			
History <sup>G</sup>	X			X			
Physical examination	X	X <sup>Q</sup>			X	X <sup>I</sup>	
Weight	X	X					
Vital signs	X	X					
Toxicity Assessment	X	X			X	X <sup>H</sup>	
Performance Status	X	X			X		
CBC, diff, platelet count	X (within 14 days)	X			X		
Na, K, BUN, Cr, AST, ALT, Bili	X (within 14 days)	X			X		
Ca, Mg, PO4	X (within 14 days)	X			X		
INR, TSH	X (within 14 days)						
Pre-Ablation labs: PLT, PT, PTT, INR				(within 2 weeks of ablation up to day of (prior to) <sup>N</sup>			

Serum Pregnancy <sup>E</sup>	X (within 7 days of drug)						
CT scan of Chest/abd/pelvis	X <sup>AC</sup> (with in 6 weeks)		X <sup>CJ</sup>		X <sup>CJ</sup> (CT does not need to be repeated if done in prior 2 months)		X <sup>D</sup>
CT scan or MRI of brain	X(within 6 weeks)		X (only if clinically indicated)		X (only if clinically indicated)		X
EKG <sup>B</sup>	X						
Survival and Disease status						X	X <sup>D</sup>

<sup>A</sup>- CT Scan for disease assessment to be performed within 6 weeks of study entry. Report required. (chest X-ray okay with baseline).

<sup>B</sup>- EKG within 8 weeks of study entry. Report required

<sup>C</sup>- An MRI or PET scan may substitute for disease assessment.

<sup>D</sup>- For patients who are removed from protocol treatment due to toxicity, without progression, Follow-up until disease progression will include CT, disease free and overall survival every 3 months (a month window is allotted for scheduling). CT scans may be done outside of the 3 month window as per MD discretion; however it is suggested that CT scans be done q 3 months. For patients who come off study for progression, overall survival is to be reported every 3 months (a month window is provided). Follow-up will be for 5 years.

<sup>E</sup> post-menopausal women (surgical menopause or lack of 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.

<sup>F</sup> 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). A physical exam within 7 days prior to cycle 1 day 1 may be utilized. PS, weight, vitals, conmeds, and AE assessment can be used from screening for cycle 1 if assessments are within 14 days of treatment. Labs and physical exam for all subsequent cycles can be within 3 days prior to day 1 of treatment. Another day is provided for holidays.

<sup>G</sup> Physician note required to be sent. For ablation time points, sites are to submit consult notes from appointment pre-ablation and if consult occurs post ablation that not is also to be sent.

<sup>H</sup> Adverse event evaluation, inclusive of SAE evaluation, will be done 30 days post last dose of drug (+1 week window). SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug, even if patient begins a new treatment. 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. It is required to inform BrUOG of patient beginning a new treatment.

<sup>I</sup> Physical to be done in coordination with 30 day toxicity assessment (+ 1 week allowed). Physical post 30 day assessments not required per study

<sup>J</sup>CT scans (or disease assessment by MRI or PET) to be completed approximately every 12 weeks (approximately every 6 cycles). For patients staying on study post initial PD – see section 7.3- next scan to confirm PD to be done in 1 month time period if patient remains on study.

<sup>K</sup>: Cycles are 14 days (+/- 3 days) however, it will not be considered a deviation if a cycle or pre-cycle assessment must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG. Cycles not to be < 10 days.

<sup>L</sup>: Sites must submit the procedure report and the imaging report from each ablation procedure to BrUOG and document response. The first ablation should be performed within 1 week (7 days) of the initial treatment with nivolumab to occur within the first cycle (14 days) of treatment. Additional ablations may be performed as per institutional standard of care. There must be a minimum of 60days between each ablation (preference is 60-90 days). This means that the first ablation will occur in cycle 1 (post receiving approximately 1 week of drug) and the sixth cycle

<sup>M</sup>: During the same procedural period as ablation, a tumor tissue biopsy may be obtained prior to each ablation for future correlative studies such as assessment of PD-L1 by immunohistochemical staining.

<sup>N</sup>: Pre-ablation labs to be done within 2 weeks of ablation (prior to). If the counts are done early and would preclude the patient from ablation, labs should be repeated on the day of the procedure prior to cancelling.

<sup>O</sup>. Optional labs: If patient agrees to optional labs; 3, 6ml purple tops will be taken before and after ablation and then post treatment. First set to be taken at baseline pre-nivolumab, second set to be taken cycle 1 pre-ablation and post Nivolumab

dosing. Third set to be taken post ablation with the pre cycle 2 nivolumab blood work. Fourth set of tubes to be taken approximately 3 months post first ablation and then fifth set to be taken approximately 3 months later, approximately 6 months after first ablation. If patient undergoes a second ablation, one set (3 purple tops) will be taken prior to ablation and one set will be taken post ablation.

P- Conmeds to be collected at baseline and then each cycle. Conmeds to also include documentation of administration of agents/drugs/topicals etc for toxicity management. Final conmed log to be sent with off study (end of treatment) materials.

Q- Physical and visit with treating MD is not required prior to each cycle dosing but may be done. It is required that the physical and visit with MD occur every other cycle however (i.e. cycle 1 (if PE not within time frames allowed from screening visit), 3, 5, 7 etc and at end of study treatment and 30 days.) All other pre-dosing assessments are required prior to each cycle.

## **6.1 Correlative Science**

PD-L1 expression may be assessed by immunohistochemistry as previously described.<sup>12,13</sup>

Optional Tumor: If optional tumor tissue is collected at the time of ablation, and stored as per routine pathology procedures at Rhode Island Hospital/Lifespan, this may be retrospectively analyzed for PDL1 expression.

Optional whole blood: Patients will have the option of providing an additional 10 cc of whole blood (3 6ml purple top tubes) to be sent to the laboratory of Dr. Loren Fast at Rhode Island hospital to assess the effect of nivolumab and ablation on lymphocyte populations. The blood will be drawn at study entry with pre-drug cycle lab work, then before and after each ablation at the times specified below.

### Correlative studies for immune function

The impact of the encounter with damaged and dying cells on the immune system can range from induction of tolerance to enhanced immune responses. One of the consequences of ablation could be enhanced tumor immunity. To test this possibility, the following correlative studies will be done at the following time-points: baseline before nivolumab, after nivolumab/ before first ablation, after ablation and prior to cycle 2 nivolumab, approximately 3 months post ablation and then approximately 6 months post ablation (approximately 3 months later). If patient has a second ablation, a set will be taken before and after ablation. At each time point 3, 6mL purple top tubes will be collected and sent to the laboratory. Initially the samples will be processed and the plasma, microvesicles and cells collected and stored at -80°C for further studies. These samples will be used to study the presence of antigen circulating in the blood, the impact of nivolumab and ablation on distribution of subpopulations based on immunophenotyping and functional studies to determine if anti-cancer immune responses have been induced by these therapeutic interventions and if detected changes correlate with response.

The blood samples when collected should be stored at room temperature, the laboratory notified (cc BrUOG on email to Dr. Fast's laboratory) and the samples transported to the laboratory for processing the same day. Research staff will not be processing samples, staff in Dr. Fast's laboratory will be processing. Samples are to be labeled with study number (BrUOG 317), patient initials, patient study number and time point.

1. Spin at 1000 rpm and collect platelet rich plasma
2. The plasma will be process further by spinning at 3000 rpm
3. The supernatant will then be centrifuged at 100000 x g for 1 hour.
4. The pellet will be resuspended in PBS containing 1% DMSO and stored at -80° C.
5. The plasma will be collected after the ultracentrifuge step and will be stored at -80° C.

6. The pellet will be resuspended in PBS containing 1% DMSO and stored at -80°C.
7. Resuspend initial cell pellet in PBS and isolate peripheral blood mononuclear cells (PBMNC) using Ficoll-Hypaque gradient density centrifugation
8. The PBMNC will be frozen down for future studies

## **7.0 RESPONSE ASSESSMENT:**

**7.1. Objective Response Rate by RECIST:** Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 will be used to assess responses by CT/ MRI but response criteria are modified by the immune-related response criteria as described in section 7.3. The first scheduled assessment of tumor response will be performed approximately 12 weeks after the first dose of nivolumab and approximately every 12 weeks thereafter. Patients in whom a scheduled scan showed initial disease progression will be allowed to continue receiving treatment until a confirmatory scan was obtained at least 1 month later. (see section 7.3)

Use of RECIST to clinically assess response for patients who progress with sum of target lesion is > 20 % then should use IrRC (if patient is asymptomatic, no vital organ involved etc.)

**7.2.** Overall responses derived from investigator reported data, with assessment according to immune-related response criteria.

## **7.3 Treatment Beyond Disease Progression**

Accumulating evidence indicated a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).

Subjects treated with nivolumab will be permitted to continue treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria: (REQUIRED for site to document and confirm all are true and submit to BrUOG)

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- A radiographic assessment/scan should be performed within 6 weeks **and at least a month after original PD to determine whether there has been a decrease in the tumor size or continued PD.** The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinical deteriorating and unlikely to receive any benefit from continued treatment with nivolumab
- If the investigator feels that the nivolumab subject continues to achieve clinical benefit by continued treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule.

**For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD.** This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short

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

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should be reported as symptomatic deterioration. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed in the study records.

#### **7.4 Modified immune-related response criteria (irRC), derived from RECIST 1.1**

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bidimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 12 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by  $\geq 20\%$ .

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

#### **Modified immune-related response criteria are defined as follows:**

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.

Overall irPR: Sum of the longest diameters of target and new measurable lesions decreases  $\geq 30\%$ .

Overall irSD: Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).

Overall irPD: Sum of the longest diameters of target and new measurable lesion increases  $\geq 20\%$  (compared to nadir). It is recommended that overall irPD be confirmed by a follow-up CT at least 4-12 from the date first documented.

Overall responses derived from changes in index, non-index, and new lesions are summarized in the table below.

**Overall Responses Derived from Changes in Index, Non-Index, and New Lesions**

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions	Non-Index Lesions	New, Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR <sup>2</sup>
Decrease 100%	Stable	Any	irPR <sup>2</sup>
Decrease 100%	Unequivocal progression	Any	irPR <sup>2</sup>
Decrease $\geq 30\%$	Absent / Stable	Any	irPR <sup>2</sup>
Decrease $\geq 30\%$	Unequivocal progression	Any	irPR <sup>2</sup>
Decrease $< 30\%$ to increase $< 20\%$	Absent / Stable	Any	irSD
Decrease $< 30\%$ to increase $< 20\%$	Unequivocal progression	Any	irSD
Increase $\geq 20\%$	Any	Any	irPD

<sup>1</sup> Decreases assessed relative to baseline

<sup>2</sup> Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

Post Ablation changes observed on radiographic studies that are larger in size than preablation masses will not be considered tumor progression if no enhancement within the lesion that suggests tumor growth.

**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:

**Kayla Rosati**  
**Director, BrUOG**  
**Brown University Oncology Research Group,**  
**Brown University**  
**Box G-R 001**  
**Providence, RI 02912**  
**Fax: 401-863-3820**  
**Phone: 401-863-3000**

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 OF 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.

FDA exemption 6/30/15, 6/30/15, 8/17/15 (for LOCR initial), Amendment #1 10/5/15 v 2 HS approval, Amendment # 2 11/9/15, 17  
Amendment #3 3/4/16, Amendment # 4 4/7/16, Amendment # 5 6/1/16 V2, Amendment # 6 7/7/16, Amendment # 7 11/16/16,  
Amendment # 8 2/22/17, Amendment #9 5/22/17

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: Subjects will be treated with 3mg/kg up to a maximum dose of 240mg of nivolumab as an approximate 60 minute IV infusion every 2 weeks.

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)

## **10.0 AGENT ACCOUNTABILITY**

Commercial nivolumab will be used in this trial, therefore there will be no drug accountability.

## **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

FDA exemption 6/30/15, 6/30/15, 8/17/15 (for LOCR initial), Amendment #1 10/5/15 v 2 HS approval, Amendment # 2 11/9/15, 18  
Amendment #3 3/4/16, Amendment # 4 4/7/16, Amendment # 5 6/1/16 V2, Amendment # 6 7/7/16, Amendment # 7 11/16/16,  
Amendment # 8 2/22/17, Amendment #9 5/22/17

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**

**An adverse event** 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).

## **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.

AEs and SAEs will be captured and reported from when the patient signs consent to 4 weeks post last dose of drug or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.

### **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 phone 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 must be reported to BrUOG within 24 hours of being made aware of the event. 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 SAEs and pregnancy reports must be reported to the Brown University Oncology Research Group to align with 24 hour notification. For pregnancy reporting time frames see section 11.3.1.

All other initial SAE information and all amendments or additions must be recorded on a MedWatch 3500A SAE form and be faxed or emailed to BrUOG within 5 business days of being made aware of the event. If the SAE is a death thought to be related to the study drug or ablation, deaths must be reported to BrUOG within 24 hours/1 business day of the investigator being made aware of the event.

BrUOG fax: 401-863-3820 Email: [Kayla\\_Rosati@brown.edu](mailto:Kayla_Rosati@brown.edu)  
[Kristen\\_Mitchell@brown.edu](mailto:Kristen_Mitchell@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.

### **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 discharge 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 (drug or ablation) must be reported within 5 business days of when the investigator is made aware of the event or as soon as the investigator is made aware of the event. Deaths that are thought to be related to drug are to be reported to BrUOG in 24 hours/1 business day of being made aware of the event. SAEs occurring within 30 days following completion of active protocol therapy (drug or ablation) will be captured even if patient begins a new treatment. AE evaluation will stop once patient begins a new treatment.

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 nivolumab or ablation (whichever is last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the study drug (or therapy/ablation) is suspected.

#### **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 contact BrUOG Central Office at (401) 863-3000 within 24 hours upon learning of the event for notification and prior to submitting the SAE report.

**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:

Brown University Oncology Research Group

Phone: (401) 863-3000, Fax: (401) 863-3820

Email: [Kayla\\_rosati@brown.edu](mailto:Kayla_rosati@brown.edu), [Kristen\\_Mitchell@brown.edu](mailto:Kristen_Mitchell@brown.edu)

All deaths during treatment or within 30 days following completion of active protocol therapy (last dose of drug or ablation) must be reported within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug or ablation, deaths must be reported to BrUOG within 24 hours/1 business day of the investigator being made aware of the event. For pregnancies please refer to prior section.

#### **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 investigational product and suspect medication
- Must type SAEs

#### **Follow-up information: \*Follow-up SAEs are required to document patient discharge or resolution of SAE event\***

Additional Info maybe added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarizing new information and faxing it with a cover letter 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).

#### **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 information. 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 Investigator Brochure. Such reports are to be telephoned or faxed to the FDA as soon as possible but no later than 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the appropriate FDA fax number.

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

#### **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. See section 7 regarding defining progression on study.**

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. Howard Safran, 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 to 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

FDA exemption 6/30/15, 6/30/15, 8/17/15 (for LOCR initial), Amendment #1 10/5/15 v 2 HS approval, Amendment # 2 11/9/15, Amendment #3 3/4/16, Amendment # 4 4/7/16, Amendment # 5 6/1/16 V2, Amendment # 6 7/7/16, Amendment # 7 11/16/16, Amendment # 8 2/22/17, Amendment #9 5/22/17

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.

**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 delivery date to the site (if applicable), inventory at the site (if applicable), 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 Brown University Oncology Research Group, as coordinator of this study, is 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 (Howard Safran, M.D.) and Brown University Oncology Research Group Director of Operations (Kayla Rosati) 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.

## **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**

The primary goal will be to determine the response rate of the combination of nivolumab and ablation.

### **17.1 Statistical Methods:**

Let 'p' be the probability of response to treatment

Null hypothesis             $H_0: p = p_0$   
Alternate hypothesis       $H_1: p >= p_1$

This study is a phase II non-randomized clinical trial. The primary endpoint of this trial is to determine the response rate for patients with metastatic non-small cell lung cancer treated with a combination of nivolumab and ablation, in the second line setting. Historically, the response rate of nivolumab alone in this setting has been about 20%.

Simon's minimax two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients, the study will be stopped early for futility. If at least 5 responses are obtained, additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 40%.

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

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

### **17.3 Laboratory Correlative Studies:**

Fisher's exact test will be used to assess the association between PD-L1 expression and objective response.

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## APPENDIX A

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

#### **BrUOG 317: Nivolumab and Ablation For Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Progressing After at Least One Prior Therapy For Metastatic Disease: A Brown University Oncology Research Group Phase II Study**

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> hospitals follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the “informed consent” process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. 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 Howard Safran MD, which is coordinated by the Brown University Oncology Research Group (BrUOG).

You are being asked to participate in this study because you have advanced non-small cell lung cancer. You have already received chemotherapy but your cancer has grown or spread despite this chemotherapy. The purpose of this study is to study the effects, good and bad, of treating one of your cancer tumors with a procedure called ablation to see if this will improve your response to a recently approved treatment for advanced lung cancer called nivolumab.

Nivolumab is an antibody (a type of human protein) that can stimulate your immune system to fight your lung cancer. Nivolumab is FDA approved to treat squamous non-small cell lung cancer.

Ablation is an FDA approved procedure to treat one or two cancer tumors in patients with limited advanced lung cancer, in which a radiologist tries to destroy a tumor by freezing it (cryoablation) or heating it (thermal ablation). The radiologist will place needles into the tumor to transmit cold, to freeze the tumor, or heat to burn the tumor.

Your doctor has suggested that you undergo ablation to treat a tumor that is causing pain or other symptoms. Ablation by itself would not be expected to extend life in patients like you with more extensive lung cancer. You and your doctor will discuss whether freezing the tumor (cryoablation) or heating the tumor (thermal ablation) is better for you. We are studying if ablation, the freezing or heating of a tumor, may make nivolumab more effective helping your immune system recognize other cancer cells and tumors as being abnormal.

We expect to enroll 33 subjects into this study and X number of patients at <INSERT HOSPITAL NAME> hospital. The study is sponsored by the Principal Investigator Howard Safran, MD and it is being coordinated by the Brown University Oncology Research Group.

### **Explanation of Procedures**

**What will happen if I take part in this research study?** If you take part in this study, you will have exams, tests and procedures to show that you can be in the study. They are part of regular cancer care.

Screening:

- Medical history prior to starting treatment.
- Physical examination, with performance status and toxicity assessment, weight and vitals
- Blood tests (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 entry
- CT scan of the chest, abdomen and pelvis within 6 weeks prior to study entry
- CT or Brain MRI within 6 weeks prior to study entry
- EKG prior to study entry, within 8 weeks

While on study:

A cycle of treatment is considered 2 weeks. You will have the following approximately every 2 weeks or as otherwise noted below:

- Performance status and toxicity assessment, weight and vitals prior to each cycle. Physical exam is required prior to every other cycle, but it may be done more frequently if the treating investigator feels it is in your best interest.
- Blood tests (approximately 3 tablespoons of blood) prior to each cycle
- CT scan of the chest, abdomen and pelvis approximately every 12 weeks (6 cycles)
- CT or Brain MRI as needed

You will receive Nivolumab through an IV (in your vein) over 1 hour in the outpatient chemotherapy clinic approximately every 2 weeks, as long as your cancer tumors do not grow or the cancer spreads to new areas of your body, for up to 2 years. Even if you are found to have progressive disease (your cancer has grown or spread), your doctor will evaluate you to see if there may be potential benefit to keeping you on the study drug. This will be discussed with you when necessary.

Ablation is performed as an outpatient in the department of radiology with both intravenous sedation and local anesthesia. The procedure takes approximately 60-90 minutes. Using CT guidance, a needle will be placed into one of your tumor masses. Your doctors will discuss with you which tumor mass in your body will undergo ablation. Ablation of a tumor mass can be performed in the lung, liver, lymph nodes, bone, and other organs.

The ablation may be performed within 7 days after the first treatment with nivolumab. Additional ablation procedures may be suggested by your doctors as part of standard treatment for your cancer if your doctors think additional ablation procedures may be of help such as to treat or prevent pain, bleeding or blockage of an organ. Each ablation must be separated by at least 60 days.

Optional Tumor Biopsy at Time of Ablation:

If you agree, during the ablation procedure, a small piece of the tumor being ablated will be taken to test the cancer cells for a protein called PD-L1, which is the target for nivolumab. These biopsies are optional and you will be given the chance to make your choice at the end of this document. The biopsy is performed under CT or ultrasound guidance using the same intravenous sedation and local anesthesia you receive for the ablation. The biopsy needle is smaller than the ablation needle.

#### Optional Blood:

You will be asked to choose if you would allow additional blood to be taken for research purposes. If you agree, an additional 1-2 tablespoons of blood will be taken with your screening blood tests before study entry and before and after ablation. Additional blood will also be taken at approximately 3 and 6 months post the first ablation. The blood will be sent to the research laboratory of Dr. Loren Fast at Rhode Island Hospital who will be researching how nivolumab and ablation affect your white blood cells.

#### Off study/Follow-up:

When you stop taking the study drug you are considered “off study” and you will then move into the follow-up portion of this trial. You will have the following exams done:

#### Off study:

- Physical examination, with performance status and toxicity assessment (and again 30 days post the last dose of drug)
- Blood tests (approximately 3 tablespoons of blood)
- CT scan of the chest, abdomen and pelvis if one has not been done in the prior 2 months
- CT or Brain MRI as needed

#### Follow-up:

- CT scan of the chest, abdomen and pelvis approximately every 3 months until your disease progresses
- CT or Brain MRI as needed

All patients will be followed approximately every 3 months for disease status and overall survival information, for up to 5 years.

#### **How long will I be in the study?**

You will receive nivolumab until your cancer starts to grow or spread for up to 2 years. An average time people will be in the study will be 6-24 months. All patients will be followed approximately every 3 months after completing or being taken off of the study treatment for up to 5 years.

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

Yes. You can decide to stop at any time. Tell the study 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 the study your doctor can evaluate doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be discussed. 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.

The study 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**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems regarding the costs of treating your cancer during this study.

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the assessment of PD-L1 in the optional tumor biopsy(ies) being collected at the time of ablation and the optional additional blood. Those services will be paid for by the study and will not be billed to you or your health insurance company.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are all study doctor visits, blood tests, treatment with nivolumab, including the drug itself and administration of the drug, ablation, drugs used to reduce side effects from nivolumab and ablation, CT scans (or MRIs) and EKGs. These services 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, you will be responsible for those costs.

**Contact Information:** If you have any questions regarding this study, you may contact the site Principal Investigator, <INSERT NAME>, MD at <INSERT PHONE NUMBER>.

### **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.

The most common side effects ( $\geq 20\%$ ) of nivolumab are:

- Fatigue
- Skin reactions: including rash, itching, hives, redness, and dry skin.
- Diarrhea or colitis (swelling of large intestine) with diarrhea
- Nausea
- Abdominal pain
- Decreased appetite
- Low red blood cells
- Fever
- Joint pain or stiffness

Less common side effects (1-20%) of nivolumab include:

- Bowel inflammation
- Liver function blood test abnormalities
- Loss of color (pigment) from areas of skin

- Dry mouth
- Stomach pain
- Vomiting
- Weight loss
- Thyroid gland abnormalities and inflammation
- Blood chemistry abnormalities, including low blood phosphate, magnesium, and potassium levels.
- High blood uric acid level
- Lung inflammation (pneumonitis - see details below)
- Cough
- Dizziness
- Headache
- Low white blood cells
- Chills
- Muscle soreness, weakness, stiffness or spasms
- Pain in arms or legs
- Tingling, burning, or numbness in hands and feet, neuropathy (including tingling, cold sensitivity, numbness, pain)
- Shortness of breath
- Abnormal taste
- Flushing
- High or low blood pressure
- Allergic reaction during or between study drug infusions
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn
- Low blood platelets (may increase risk of bleeding)

Rare (<1%) but potentially serious side effects of nivolumab include:

- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix
- Increase in inflammatory blood proteins (e.g., lipase)
- Adrenal gland abnormalities
- Pituitary gland inflammation
- Changes in vision (including decreased or blurry vision), inflammation of the eye, or bleeding into the eye
- Liver inflammation
- Acute kidney injury, failure, inflammation (nephritis)
- Abnormal blood cell production
- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms, or legs
- Inflammation of the pancreas
- Back pain

- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Inflammation of the heart or its lining
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections, and skin infections.
- Decreased movement of the intestines
- Disorientation
- Swelling of the optic disc
- Inflammation of the optic nerve
- Inflammation of the lining of the brain and spinal cord
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Hepatitis

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

Nivolumab 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.

By signing this document you understand that there is no known potential for the use of ablation (ablating one lesion in a patient who may have diffuse metastatic disease) to increase your survival. It is hoped that ablation may increase the likelihood of your cancer responding to nivolumab. By signing this form you agree to accept the risks of the ablation procedure without any known survival benefit.

### **Risks From Ablation:**

Side effects from ablation differ depending on the location in the body the ablation is being performed. Please review with your doctor the expected risks to you of ablation. General risks of ablation include the following:

#### **The most common side effects (> 20%) of ablation are:**

Pain  
Bruising  
Bleeding  
Fatigue  
Weakness

#### **Less common side effects (1-20%) of ablation include:**

Shortness of breath  
Collapse of a lung that will need temporary placement of a chest tube.  
Infection  
Temporary changes in your body chemistries such as your potassium or other electrolytes

**Rare (<1%) but potentially serious side effects of ablation include:**

Damage to nerves

Liver or kidney damage

**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.

**Radiation Risks**

If you participate in this study, you receive several medical imaging scans that involve radiation exposure:

- CT guidance during ablation procedure
- Chest-abdomen-pelvis CT scan at screening, every 12 weeks thereafter, possibly at the end of treatment, and then every 3 months until progression of your disease.
- CT scan of your brain at screening and whenever clinically indicated

You may be wondering if this amount of radiation exposure carries any additional risk of cancer in the future.

- The State and Federal government has established yearly limits of radiation exposure for people (radiation workers) who work around radiation every day
- There has been no increased rate of cancer for radiation workers compared to others
- If enrolled into this study, the maximum radiation exposure you are expected to receive during your first year on the study is about equal to the annual radiation exposure limit for a radiation worker
- The maximum radiation exposure you are expected to receive during your second and following years on the study is about one half (1/2) of the annual radiation exposure limit for a radiation worker
- At this level of radiation exposure, your increased risk of cancer due to this radiation is low
- Please note that this is a long-term risk; that is, cancers that are known to be caused by radiation generally do not appear for 7 to 50 years after the exposure
- If you have concerns about the radiation exposure associated with this study, please speak with your doctor

**Risk of Biopsies:** Risks associated with biopsies include pain, redness, swelling, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site. In patients who undergo a biopsy during a procedure called a bronchoscopy, the risks also include lung collapse.

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**

It is hoped that the combination of nivolumab and ablation will be able stimulate your immune system against your cancer. Taking part in this study may or may not make your health better. This information could help future cancer patients. The benefits of this research include learning more about Nivolumab and ablation in treating certain lung cancer tumors.

### **Alternative Therapies**

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

- Getting treatment or care for your cancer without being in a study such as receiving other chemotherapy or nivolumab alone
- Receiving radiation treatments.
- Taking part in another study
- Getting no treatment
- Being followed closely and deciding about being treated when the disease progresses further

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 the Principal investigator and sponsor, Dr. Howard Safran 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>, in the <INSERT HOSPITAL NAME> Office of Research Administration, at <INSERT PHONE NUMBER>

### **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: The Sponsor: Principal Investigator Howard Safran, MD, BrUOG, the coordinating office, or their 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.

For more detail about your privacy rights see the <INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

## RELATED STUDIES

**Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.**

**You can say “yes” or “no” to the following studies. Below, please mark your choice for each question.**

When having ablation your doctors may want to take a biopsy of your tumor to test it for the expression of a protein called, PDL-1. They may also check the tumor for other immune cells. Your doctors are hoping that they may be able to see if the levels of the protein, PD-L1 other immune markers and immune cells are related to how you respond to this treatment with Nivolumab and ablation. Leftover tissue may be saved in a specimen bank to allow for future unknown testing on your tumor tissue. This may allow your doctors to use some of your collected tissue for research to learn more about your disease and potential treatment options and responses.

### **Benefits**

The benefits of this research include learning more about Nivolumab and ablation in treating certain lung cancer tumors.

### **Risks**

Risks associated with taking a biopsy at the time of ablation include:

Unlikely risks include bleeding, pain and unsuccessful biopsy (your doctor is not able to obtain enough tissue).

## GINA STATEMENT

This study involves ‘genetic testing’ as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA’s protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA’s protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL NAME>’s privacy policies generally protect the privacy of such information and restrict its release outside of <INSERT HOSPITAL NAME>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse at <INSERT PHONE NUMBER>.

These reports will not be put in your health record. No matter what you decide to do, it will not affect your care.

Optional tumor tissue:

1. A biopsy of my tumor tissue may be taken at the time of my ablations to evaluate for PD-L1, other immune markers and immune cells.
  - Yes  No
2. A portion of my tumor tissue may be saved for specimen banking at Rhode Island Hospital and for additional future testing. I understand that I will not be informed of any information that is discovered from these tests.
  - Yes  No

Optional Blood:

1. Additional laboratory samples, (approximately two tablespoons of blood) can be drawn at the following time points: at baseline when I am being evaluated for this trial, before and after ablation and approximately 3 and 6 months after my first ablation. If I undergo additional ablation procedures additional laboratory samples (approximately two tablespoons of blood) may also be taken before and after ablation. I understand that the additional blood work will be sent to the research laboratory of Dr. Loren Fast at Rhode Island Hospital to study the effect of nivolumab and ablation on my blood cells.
  - Yes  No

**Participation in Specimen Banking**

You are agreeing to participate in this research study by signing this form (the “Main Study”) **tissue** samples will be collected from you, which will be referred to here as your ‘Specimen.’ In addition to being analyzed as part of the Main Study, your Specimen may be useful for future research purposes. You are being asked to agree to this optional component (the “Specimen Banking Component”) of the study if you are willing to allow your Specimen to be saved or ‘banked’ for use in future research studies. If you agree to this optional Specimen Banking Component, you give permission for your Specimen to be stored in a specimen bank indefinitely, until it is no longer usable. The Specimen may also be used to create a cell line, which would also be stored for an indefinite period of time. . Along with the specimens, portions of your personal health information collected as part of the Main Study will also be stored. Your Specimen and personal health information may be stored and analyzed at Lifespan; or, they may be shared with researchers at other institutions or companies that may store them and use them for their own research. It is very unlikely that any future research performed using your Specimen would benefit you directly. However, the research may provide important medical knowledge that in the future could help other patients with your medical condition or other medical problems.

At this time, we do not know what future research studies may be done using your Specimen. Such research studies may include genetic tests that would analyze your DNA, RNA or other gene products, like proteins and metabolites. These genetic tests may be done by Lifespan, or they may be done by other researchers with whom your Specimen and data have been shared. Because any genetic testing of your Specimen would be for research purposes, the results would have no clear implications for your health or medical condition, or that of your family members. Any testing results would not be made available to you or to any insurance company, your employer, your family, or any physician who treats you in the future.

There is a very remote possibility that your Specimen and some associated data may become part of a process or product that ultimately has commercial value. For instance, the Specimen could be used to establish a cell line (a group of cells that are able to reproduce, sometimes indefinitely)

that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you decide at some time in the future that you no longer wish your stored Specimen to be used in future studies, you have the right to request that the Specimen be withdrawn from the specimen bank. However, withdrawal cannot be guaranteed and may be impossible. For example, it is possible that the Specimen might no longer be identifiable as belonging to you, or it may have been used up, or it may already have been shared with other institutions or companies for their own research. To request withdrawal of your Specimen, please write to: Howard Safran, MD 593 Eddy Street APC1 Providence, RI 02903.

Refusal to participate in this optional Specimen Banking component will in no way affect your ability to receive any treatment or services offered as part of the Main Study, and will not have any effect on your other health care, the payment for your health care, or your health care benefits.

**If you are willing to allow your Specimen to be banked for future research purposes, please indicate your consent by signing below.**

\_\_\_\_\_  
Signature of study volunteer/authorized representative

\_\_\_\_\_  
Date

**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  
signed

\_\_\_\_\_  
Date

\_\_\_\_\_  
and Time when  
signed

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

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APPENDIX B: Checklist

**Nivolumab and Ablation For Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Progressing After at Least One Prior Therapy For Metastatic Disease: A Brown University Oncology Research Group Phase II Study**

**Inclusion Criteria**

- \_\_\_\_\_ (y/n) Pathologically or cytologically confirmed NSCLC
- \_\_\_\_\_ (y/n) Stage IIIB or stage IV.
- \_\_\_\_\_ (y/n) Progression after at least 1 line of systemic treatment (IV or oral) for metastatic or locally advanced disease. Patients progressing within 6 months of completion of neoadjuvant or adjuvant chemotherapy are also eligible. Radiation does not count as 1 line.
- OR
- \_\_\_\_\_ (y/n) Patients progressing within 6 months of completion of neoadjuvant or adjuvant chemotherapy are also eligible without having treatment for metastatic disease (for example patient with stage I disease undergoes resection, receives systemic chemotherapy and then progresses to the liver (now stage IV) within 6 months of chemotherapy). Radiation does not count as 1 line.
- \_\_\_\_\_ (y/n) At least 1 site of measurable disease that will not be treated with ablation
- \_\_\_\_\_ (y/n) Ablation for advanced lung cancer is being considered by the treating physician for treatment or prevention of symptoms such as pain, bleeding or obstruction. Documentation to be sent in writing from MD to confirm criterion.
- \_\_\_\_\_ (y/n) At least 3 weeks since prior systemic treatment and/or radiation therapy for patient's NSCLC (from treatment day 1 on study)
- \_\_\_\_\_ (y/n) No brain metastases except for patients whose metastases have been removed by surgical resection or have had stereotactic radiation or gamma knife with no evidence of active disease on MRI within 28 days of starting treatment.
- \_\_\_\_\_ (y/n) Voluntary, signed written informed consent, Date signed \_\_\_\_\_
- \_\_\_\_\_ (y/n) Age  $\geq 18$
- \_\_\_\_\_ (y/n) ECOG PS 0-2
- \_\_\_\_\_ (y/n) Life expectancy  $\geq 12$  weeks (must be confirmed by treating MD in writing)
- \_\_\_\_\_ (y/n) Must be willing to consent to use effective contraception while on treatment and for at least 2 months afterwards.
- \_\_\_\_\_ (y/n) CT scan of the chest/abdomen/pelvis within 6 weeks of study entry. Patients can have PET/MRI of the chest/abdomen instead. Chest Xray okay.
- \_\_\_\_\_ (y/n) EKG within 8 weeks study entry
- \_\_\_\_\_ (y/n) Absolute neutrophil count  $\geq 1,000/\text{ul}$ , Date \_\_\_\_\_
- \_\_\_\_\_ (y/n) Platelet  $\geq 75,000/\text{uL}$ , Date \_\_\_\_\_
- \_\_\_\_\_ (y/n) Total bilirubin  $\leq 1.5 \times \text{ULN}$ , Date \_\_\_\_\_
- \_\_\_\_\_ (y/n) AST  $\leq 3 \times \text{ULN}$
- \_\_\_\_\_ (y/n) Creatinine  $\leq 1.5 \text{ mg/dl}$  or creatinine

**Exclusion Criteria:**

- \_\_\_\_\_ (y/n) Patients with a history of clinically significant chronic autoimmune disease

\_\_\_\_\_(y/n) Prior therapy with antibodies that modulate T-cell function (e.g., anti-CTLA-4, anti-PD-1, and anti-PD-L1)

\_\_\_\_\_(y/n) Conditions currently requiring immunosuppressive medications

\_\_\_\_\_(y/n) Known history of HIV or hepatitis B or C

\_\_\_\_\_(y/n) Bleeding diathesis or coagulopathy that would prevent cyroablation from being safely performed.

\_\_\_\_\_(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 organ allograft even if not taking immunosuppressive medications

\_\_\_\_\_(y/n) Pregnant or breastfeeding.

Optional tumor tissue:

Did patient agree to optional biopsy of tumor tissue at time of ablation?

Yes  No

Did patient agree that a portion of the tumor tissue could be saved in the specimen bank at RIH?

Yes  No  N/A

Did patient agree to optional laboratory correlative samples?  Yes  No

Document if patient will undergo Cryoablation or thermal ablation: \_\_\_\_\_

**\*\*Remember to document which lesion will not be ablated for registration\*\***

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						

IRB approval date of protocol: \_\_\_\_\_

Hospital where patient will be treated with Oncologist: \_\_\_\_\_

Hospital where ablation will occur: \_\_\_\_\_

Date patient will begin treatment: \_\_\_\_\_ Date patient to undergo ablation: \_\_\_\_\_  
Primary Physician: \_\_\_\_\_ Primary Diagnostic Radiologist: \_\_\_\_\_

Your signature: \_\_\_\_\_

**APPENDIX C**  
**NCI CTC Version 4**

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC 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 CTC Version 4

**APPENDIX D**  
**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 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 E**

**CASE REPORT FORMS**

Attached separately are the BrUOG Case Report Forms