A Phase II trial of surgery and stereotactic radiosurgery with neoadjuvant nivolumab and ipilimumab in patients with surgically-resectable, solid tumor brain metastases (NCT04434560)

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

Sponsor:	PI – Duke Cancer Institute
Funding Source:	Translating Duke Health Funding
Drug Source:	BMS
Protocol Source:	PI - Duke Cancer Institute
Duke IRB#:	Pro00103812
BMS Protocol #:	CA184-583
IND#	147565

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Version: 1.0	10/07/2019	Original draft sent to BMS
Version: 1.1	12/02/2020	Updated based on BMS' comments from 11/06/2019
Version: 1.2	03/20/2020	Revised serum creatinine per FDA recommendation
Version: 1.3	06/15/2020	Addition of table in Section 6, updated face page
Version: 1.4	08/31/2020	Revised schedule of events and eligibility
Version: 1.5	09/29/2020	Removed melanoma BRAF status for eligibility
Version: 1.6	02/11/2021	Revised schedule of events and eligibility
Version: 1.7	03/19/2021	Removal of control arm

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4. LIST OF ABBREVIATIONS

AE	Adverse Event
BMS	Bristol-Myers Squibb
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
GBM	Glioblastoma
IV (or iv)	Intravenously
ICS	Investigational Chemotherapy Service
IO	Immunotherapy
IRAE	Immune Related Adverse Event
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PRTBTC	Preston Robert Tisch Brain Tumor Center
RCC	Renal Cell Carcinoma
SAE	Serious Adverse Event
SD	Stable Disease
SRS	Stereotactic Radio Surgery
TNBC	Triple Negative Breast Cancer

5. PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

5.1. Purpose

A phase II study of neoadjuvant nivolumab and ipilimumab in patients with surgically-resectable, solid tumor brain metastases is planned to address the following objectives.

Primary Objectives:
1. Assess the feasibility of neoadjuvant ipilimumab and nivolumab treatment before surgery and SRS in patients with solid tumor brain metastases as measured by the proportion of patients who have their surgery delayed or surgery never occurs.
2. Demonstrate that neoadjuvant immunotherapy will increase proliferation of circulating T-cells compared to baseline measurements.

Exploratory Objectives:
1. Describe the survival of patients with solid tumor brain metastases receiving neoadjuvant ipilimumab and nivolumab followed by surgery and SRS.
2. Describe the time to local intracranial progression.
3. Describe the time to distant intracranial progression.
4. Describe the time to overall intracranial progression.
5. Describe progression-free survival.
6. Quantify the rate of radiation necrosis.
7. Describe the immune expression profile of patients treated with neoadjuvant ipilimumab and nivolumab.

Hypotheses
This is a hypothesis testing protocol designed to test the following hypotheses:
1. Neoadjuvant immunotherapy will not delay surgical resection for patients with solid tumor brain metastases.
2. Neoadjuvant immunotherapy will increase Ki67 on circulating PDL-1+/CD8+ T-cells among patients with solid tumor brain metastases.

5.2. Background and Significance

As treatments for primary tumors improve and patients survive longer, the potential for primary tumors to metastasize increases, creating a need for newer and better therapeutic strategies for patients with metastases. Currently, up to 30% of cancer patients will develop at least one brain metastasis [1]. Current standard of care therapies include resection and stereotactic radiosurgery (SRS) followed by a variety of maintenance treatments. Progression free survival (PFS) and overall survival (OS) rates for patients with brain metastases are modest at best. For example, lung

cancer, breast cancer and melanoma patients with untreated metastases have median survival rates of 12 months [2], 13.8 months [3, 4], and 9.8 months [5], respectively, motivating a need for novel therapeutic approaches within these patient populations. Recent approaches for treating brain oligometastases (few, small metastases) include immunotherapies, but the timing as to when to initiate immunotherapy is still up for debate. Most studies have focused on adjuvant immunotherapies, following surgical resection and SRS; however, giving immunotherapies after surgery may reduce T-cell receptor modulation, activating fewer tumor-specific T cells leading to a less robust immune response. Providing immunotherapies in the neoadjuvant setting, where antigenic burden is higher in the brain, could result in enhanced T-cell receptor modulation, and therefore more robust activation of tumor-specific T cells and an overall more effective immune response. Indeed, a limited number of studies have shown improved outcomes for patients receiving immunotherapy in the neoadjuvant setting, demonstrating neoadjuvant immunotherapy merits further investigation.

The two most common immunotherapy checkpoint blockades are PD-1/PD-L1 and CTLA-4. Bristol Meyers Squibb (BMS) has developed compounds targeted at blocking each of these checkpoints: nivolumab (PD-1) and ipilimumab (CTLA-4). This is a feasibility and efficacy study testing the combination of neoadjuvant nivolumab and ipilimumab in patients with solid tumor brain oligometastases as described in Section 5.3.

5.3. Design and Procedure

After providing informed consent, up to 20 eligible participants with surgically-resectable, solid tumor brain metastases will be treated. Participants will receive a single dose of neoadjuvant nivolumab and ipilimumab 7 days (± 3 days) prior to surgical resection. Nivolumab will be given at the FDA-approved dose of 3 mg/kg; ipilimumab will be given at the FDA-approved dose of 1 mg/kg. Patients will then continue to have standard of care SRS 3 weeks (±3 weeks) after surgery. See Section 6 for the study schema.

5.4. Selection of Subjects

Please see Section 11 for a list of all inclusion and exclusion criteria.

5.5. Duration of Study

Patients will be on study for up to 18 months after initiation of study treatment.

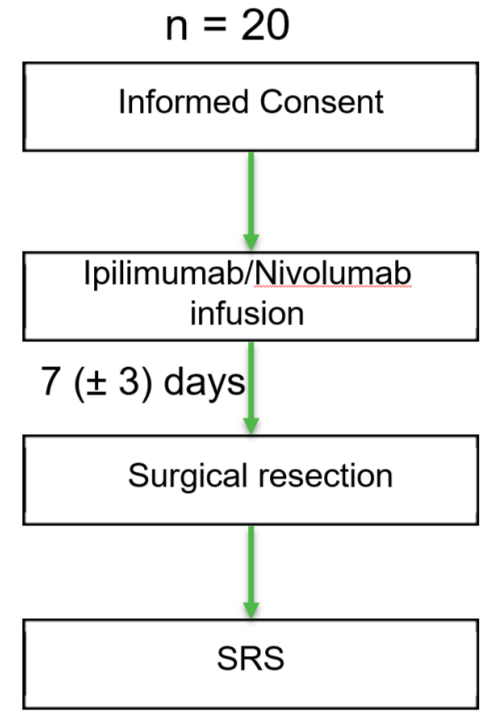
5.6. Data Analysis and Statistical Considerations

Feasibility will be assessed by the proportion of patients who have their surgery delayed. With the checkpoint inhibitors being administered on Day -7, the surgery is scheduled for Week 1, Day 1 (± 3 days). *Surgery will be considered delayed if it never occurs or occurs after Day 4 (i.e. Day 1 + 3)*. The proportion of patients experiencing surgical delay as defined in Section 15.5.1.1 will be computed as the number of patients with delay divided by the total number of patients per arm. Methods developed for continuous monitoring of toxicity will assess whether the number of surgical delays is excessive. Monitoring rules based upon Pocock monitoring rules are provided in Section 15.5.1.2.

A one-sample t-test will assess whether significant changes fold-change in Ki67 levels between baseline and Day 1 occurred.

Kaplan-Meier methodology will be used to graphically display survival and progression-free survival; whereas, cumulative incidence curves will be used to graphically display time to local intracranial progression, time to distant intracranial progression, and time to overall intracranial progression as defined in Section 15.6.2.

6. STUDY SCHEMA



Arm	Study Drug	Study Drug Administration Schedule	Dose
1	Nivolumab	7 days (±3 days) prior to surgery	3 mg/kg
1	Ipilimumab	7 days (±3 days) prior to surgery	1 mg/kg

7. BACKGROUND AND SIGNIFICANCE

7.1. Study Disease

Brain metastases are 10 times more common than primary brain tumors and arise in 10-35% of adult cancer patients [6], affecting approximately 200,000 adult cancer patients each year in the US [7]. Though brain metastases can develop from any primary tumor, the most frequent primary tumors to metastasize to the brain originate in the lung, skin (melanoma), kidney, and breast [7]. Given the heterogeneity of brain metastases, prognosis varies widely (anywhere from a few months to over a year), and is largely dependent on neurological performance status at the time of diagnosis, and the primary tumor location [6]. In a recursive partitioning analysis of prognostic factors in patients with brain metastases, the best median survival was 7.1 months, while the worst median survival was 2.3 months [8]. According to a multicenter, retrospective analysis of 3940 patients with brain metastases, median overall survival varied with primary tumor location, with a median OS of 7 months for NSCLC, 6.74 months for melanoma, 9.63 months for RCC, and 13.8 months for breast cancer [9]. Despite evolution of the standard of care for patients with brain oligometastases from whole brain irradiation and systemic therapy to include some combination of surgical resection, SRS, and carefully selected systemic therapy [7], prognosis remains poor for these patients with a median survival of around 10.8 months [10]. Clearly, there is a need to identify new therapies for patients with brain oligometastases.

7.2. Study Agent

Immunotherapies, including checkpoint inhibitors, have shown promise for treating a variety of tumors, including CNS tumors [11]. The PD-1/PD-L1 and CTLA-4 checkpoint blockades are often responsible for preventing an effective anti-tumor immune response by inducing T-cell senescence. Checkpoint inhibitors, such as pembrolizumab (Keytruda®) and nivolumab (Opdivo®), inhibit PD-1 on T-cells to delay T-cell senescence by disrupting PD-1/PD-L1 interaction. Other checkpoint inhibitors, like ipilimumab (Yervoy®), bind to CTLA-4 on T-cells to prevent T-cell inactivation, promoting a more robust immune response. Both nivolumab and ipilimumab currently have FDA approval for various indications outlined in Sections 7.2.1 and 7.2.2. Nivolumab and ipilimumab will be administered a single time at the FDA approved doses of 3 mg/kg and 1 mg/kg, respectively.

7.2.1. Nivolumab

Nivolumab (Opdivo®) is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). Nivolumab is currently FDA approved for unresectable, metastatic, and progressive melanoma and progressive metastatic squamous non-small cell lung cancer. For further details regarding nivolumab, including its physical properties, pharmaceutical properties, pre-clinical studies, and toxicology, please refer to the Investigator's Brochure.

7.2.2. Ipilimumab

Ipilimumab (Yervoy®) is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is currently FDA approved unresectable, metastatic, or cutaneous melanoma; advanced renal cell carcinoma in combination with nivolumab; microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed. For further details regarding ipilimumab, including its physical properties, pharmaceutical properties, pre-clinical studies, and toxicology, please refer to the Investigator's Brochure.

7.3. Study Purpose/Rationale

Treatment of a limited number of brain metastases includes a mélange of focused radiotherapy, neurosurgical resection, and carefully selected systemic therapy. The advent of immunotherapies merits new investigations into the order and timing of standard of care and novel approaches. In an article published in the New England Journal of Medicine, Tawbi et al report that systemic treatment of asymptomatic melanoma brain metastases with ipilimumab and nivolumab showed clinically significant intracranial responses with complete response rate of 26% [12]. Patients with symptomatic brain metastases have inferior intracranial response rates and are in need of novel strategies [13]. A similar study published in The Lancet Oncology showed clinical response of both melanoma and NSCLC metastatic to the brain to pembrolizumab (PD-1 inhibitor) treatment [14]. These response rates are respectable but leave room for improvement. Single agent PD-1 inhibition with nivolumab was ineffective in brain metastases from renal cell carcinoma with intracranial response rates of only 12% [15]. While the above trials have focused on adjuvant immunotherapy, the intent of the proposed study is to determine whether neoadjuvant immunotherapy would improve upon the current standard of care in patients with newly diagnosed brain metastases. Giving immunotherapies after surgery reduces T-cell receptor modulation, activating fewer tumor-specific T cells leading to a less robust immune response (Figure 1).

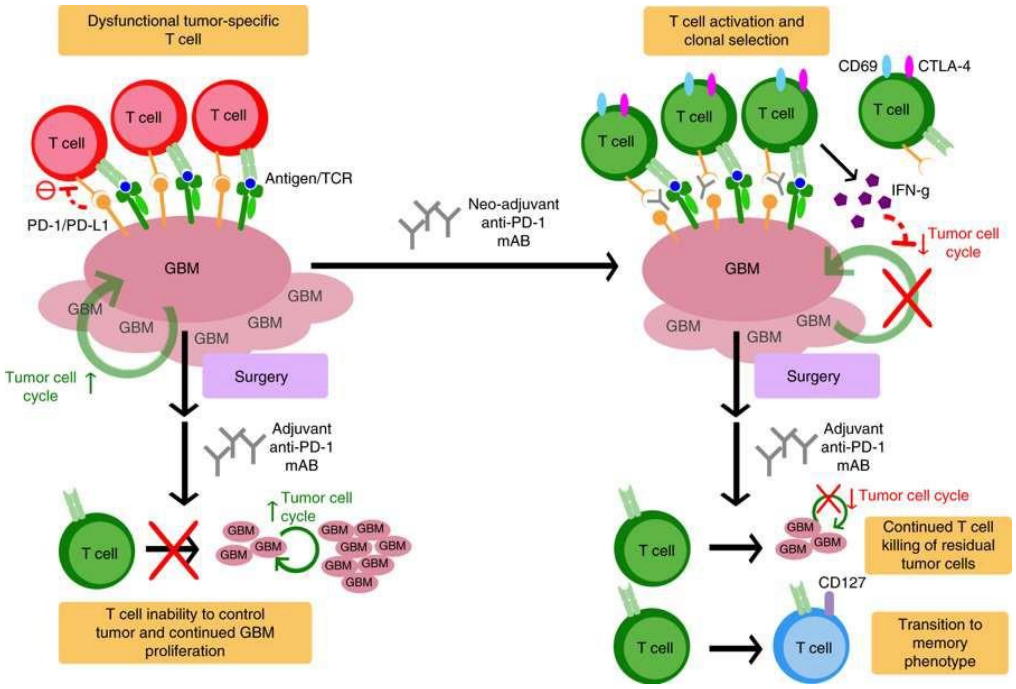


Figure 1: Proposed mechanism for neoadjuvant immunotherapy t-cell modulation in GBM. Taken from Cloughesy et. al.

Providing immunotherapies in the neoadjuvant setting, where antigenic burden is higher, should result in enhanced T-cell receptor modulation within the brain, and therefore more robust activation of tumor-specific T cells and an overall more effective immune response. Cloughesy et al reported in Nature Medicine that neoadjuvant treatment of surgically-resectable glioblastoma (GBM) with pembrolizumab resulted in significantly extended overall survival compared to patients who received adjuvant pembrolizumab (Figure 2) [16].

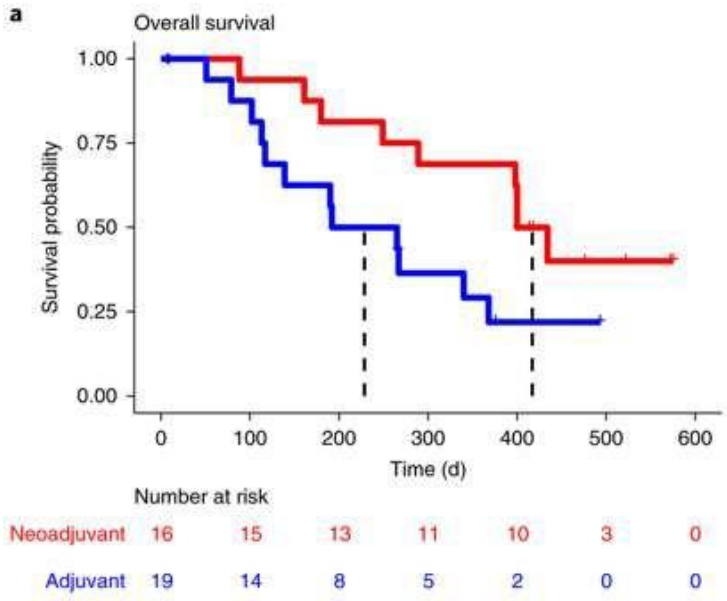


Figure 2: Neoadjuvant treatment of surgically-resectable GBM with pembrolizumab results in significantly extended survival compared to adjuvant treatment. Adapted from Cloughsey et al.

Importantly, **no patients in the neoadjuvant group experienced surgical delay**, suggesting that administration of checkpoint inhibitors prior to surgical resection is safe.

Given that immunotherapy, specifically nivolumab and ipilimumab, have been shown to have significant anti-tumor activity in brain oligometastases [12], and that administration of checkpoint inhibitors prior to surgery results in improved overall survival in patients with GBM [16], investigating the timing of immunotherapy administration in patients with brain metastases is clinically important. Towards this end, we have designed a single-arm clinical trial of neoadjuvant nivolumab and ipilimumab in patients with asymptomatic or minimally symptomatic brain metastases known to have spread from primary tumors that are traditionally responsive to immunotherapies. The percentage of patients experiencing surgical delay in the neoadjuvant treatment arm will be recorded to assess feasibility. Immunotherapy activity will be established by assessing the change in T-cell proliferation levels in circulation between baseline and Day 1 (see Section 12.7.5).

8. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	Assess the feasibility of neoadjuvant ipilimumab and nivolumab treatment before surgery and SRS among patients with solid tumor brain metastases	Among eligible patients, the percentage of patients who experience surgical delay. Surgery is considered delayed if it occurs more than 10 days after ipilimumab and nivolumab, or never occurs, for reasons relating to the immunotherapy treatment.	See Section 15.5.1
Other Primary	Demonstrate that neoadjuvant immunotherapy will increase proliferation of circulating T-cells compared to baseline measurements	Mean fold-change between baseline and day 1 in Ki67 levels	See Section 15.5.2
Exploratory	Describe the survival of patients with solid tumor brain metastases receiving neoadjuvant ipilimumab and nivolumab followed by surgery and SRS.	Median survival	See Section 15.6.1
Exploratory	Describe the time to local intracranial progression	Median time to local intracranial progression	See Section 15.6.2
Exploratory	Describe the time to distant intracranial progression	Median time to distant intracranial progression	See Section 15.6.2
Exploratory	Describe the time to overall intracranial progression	Median time to overall intracranial progression (local or distant)	See Section 15.6.2
Exploratory	Describe progression-free survival	Median progression-free survival	See Section 15.6.2
Exploratory	Quantify the rate of radiation necrosis	Percent of patients with radiation necrosis	See Section 15.6.3
Exploratory	Describe immune express profiles	Normalized immune expression	See Section 15.6.4

9. INVESTIGATIONAL PLAN

9.1. Study Design

This is a phase 2 study that assesses the feasibility and efficacy of neoadjuvant immunotherapy in patients with previously untreated, surgically-resectable, solid tumor brain metastases. Histologic types are restricted to those known to extracranially respond to immunotherapy, and will include, but not be limited to, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC without known

ALK+, EGFR+, and ROS alterations, renal cell carcinoma (RCC), melanoma, and triple negative breast cancer (TNBC) that is PD-L1 positive, ovarian carcinoma, and urothelial carcinoma

Eligible participants will receive a single infusion of nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg 7 days (±3 days) prior to surgical resection of their metastases. Patients will then receive SRS 3 weeks (±3 weeks) after surgery. Patients will be followed for 18 months after initiating study treatment. Up to 20 participants will be recruited and treated. Blood will be collected periodically during the study for correlative assessments as described in Section 12.7.5.

9.1.1. Definition of Dose-Limiting Toxicity (DLT)

Not applicable.

9.1.1.1. Non-hematologic:

Not applicable.

9.1.1.2. Hematologic:

Not applicable.

9.1.1.3. Other Considerations:

Not applicable.

9.1.2. Dose Modification

9.1.2.1. Non-hematologic:

Not applicable, only one dose of the study drug is given so there will be no intra-patient dose reduction. Similarly, the proposed doses of 3 mg/kg for nivolumab and 1 mg/kg for ipilimumab are recommended by the FDA.

9.1.2.2. Hematologic:

Not applicable, only one dose of the study drug is given so there will be no intra-patient dose reduction. Similarly, the proposed doses of 3 mg/kg for nivolumab and 1 mg/kg for ipilimumab are recommended by the FDA.

9.1.2.3. Other considerations:

Not applicable, only one dose of the study drug is given so there will be no intra-patient dose reduction. Similarly, the proposed doses of 3 mg/kg for nivolumab and 1 mg/kg for ipilimumab are recommended by the FDA.

9.1.3. Safety Considerations

Nivolumab safety: The most common adverse reactions in cancer subjects in other clinical trials with nivolumab include fatigue; skin reactions including rash, itching, hives, redness, and dry skin; diarrhea; nausea; abdominal pain; decreased appetite; low red blood cells; fever; and joint pain or stiffness. Less common side effects include bowel inflammation, lever function blood test abnormalities, loss of color (pigment) from areas of skin, dry mouth, vomiting, weight loss, thyroid gland abnormalities, blood chemistry abnormalities, high blood uric acid level, lung inflammation (pneumonitis), cough, dizziness, headache, low white blood cells, chills, muscle soreness, muscle weakness, stiffness, muscle spasms, paralysis, pain in arms or legs, tingling in hands and feet, burning in hands and feet, numbness in hands and feet, 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, and low blood platelets. Rare, but potentially serious side effects 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; adrenal gland abnormalities; pituitary gland inflammation; liver inflammation; changes in vision, inflammation of the eye, or bleeding into the eye; acute kidney injury or failure; 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; 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 and skin infections; decreased movement of the intestines; disorientation; swelling of the optic disc; inflammation of the optic nerve; inflammation or loss of the lining of the brain and spinal cord; Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); central demyelination; abnormal brain function due to brain inflammation; rhabdomyolysis; polymyositis; and toxic epidermal necrolysis. Nivolumab can cause fetal harm when administered to pregnant women. Females of reproductive potential should use effective contraception while on treatment with nivolumab and for at least 5 months after the last dose. For additional information about nivolumab safety and adverse event management, please see Section 18.1.

Ipilimumab safety: Ipilimumab has been most frequently studied in subjects with advanced melanoma. Other studies have been conducted in subjects with prostate cancer and lung cancer. In previous studies in subjects with advanced melanoma, approximately 79-80% experienced a side effect from ipilimumab. Most were mild to moderate and resolved with proper medical treatment. Side effects that may occur during the infusion of ipilimumab include fever, hypotension, chills, flushing, nausea and/or vomiting. If an infusion reaction occurs, the infusion will be slowed or stopped until the symptoms have been treated. These symptoms can also occur hours after the completion of the infusion. The most common side effects of ipilimumab include diarrhea, fatigue, skin itchiness, skin rash, nausea, fever, decreased appetite, vomiting, colitis,

abdominal pain, headache, constipation. Less common side effects include chills, weakness, muscle pain, and redness of skin. Rare side effects (in less than 1% of subjects) include tumor lysis syndrome, which can result in elevation in certain blood levels (for example, uric acid, phosphorous, potassium) can cause the kidneys to shut down, the heart to function irregularly (for example, an irregular heartbeat), shortness of breath, and loss of consciousness.

Ipilimumab can cause side effects due to the immune system attacking normal cells, called immune-related adverse events or IRAEs. In previous studies in subjects with advanced melanoma, 72-76% of treated subjects developed an IRAE of any grade of severity. About 25-37% of subjects had a severe IRAE. These IRAEs have usually been controlled by stopping ipilimumab temporarily or permanently and if needed, with medications, including steroids (medications that are used to decrease inflammation).

For additional information about ipilimumab safety and adverse event management, please see Section 18.2.

Surgical Complications: The surgical resection carries a risk for cerebrospinal fluid leak, infection, hemorrhage, loss of neurologic function, non-neurologic complications, and death. These risks depend primarily on the preoperative condition of the patient, the size and location of the tumor and associated diseases. The potential risk for the patient will be discussed in detail with the patient and family.

Stereotactic radiosurgery (SRS): Side effects resulting from complications of SRS include tiredness and fatigue, headache, nausea, vomiting, reddening of the skin of the scalp, memory or neurological problems (rare), and late development of a second cancer (rare).

Anesthesia: Patients undergoing general anesthesia may be subjected to associated risks including pneumothorax, pneumonia, airway injury, hypotension, myocardial infarction, stroke, hepatic and renal injury and death.

Peritumoral Inflammation and Increased Intracranial Pressure: Peritumoral inflammation may be secondary to the disease process itself, the surgical procedure, necrosis from radiation, or inflammation due to immune infiltration of the brain or destruction of tumor cells. Symptoms may include, but are not limited to, severe headache, confusion, lethargy, unresponsiveness, coma, or focal neurological deficits. Patients will be monitored throughout the course of the study for peritumoral inflammation and upon any signs or symptoms of cerebral edema, may have their steroid doses increased or receive treatment with an antiangiogenic agent, osmotic diuretic, or surgical decompression. Edema that fails to respond to aggressive therapy may lead to permanent neurological impairment. The risks will be discussed with the subject and the subject's family.

Risk of Phlebotomy: Drawing blood or inserting an intravenous catheter into an arm vein may result in bruising or swelling in the area of the insertion, bleeding at the site of the needle puncture, light headedness, fainting and very rarely, local infection, which may be severe. These risks are reduced by the fact that the blood will be drawn by a qualified physician, nurse or phlebotomist (a professional trained to draw blood).

Risks of MRIs: Risks and/or discomforts associated with MRI scans include anxiety produced from being in a tight, enclosed space (claustrophobia). In addition, the machine operates using a large and powerful magnet, which attracts certain metals. Therefore, people with these metals in their bodies (specifically pacemakers, infusion pumps, metal aneurysm clips, metal prostheses, joints, rods or plates) will be excluded from the study. Patients will also be checked to make sure that they do not bring any metal objects into the MRI facility. Dental fillings are less affected by the magnetic fields generated and are therefore permitted. Patients will be asked to let the physicians conducting this study know of any metal in their bodies other than dental fillings.

Unknown Risks: The overall risk classification of this research is unknown.

9.1.4. Missed Doses

Not applicable as there is only one dose of the study agents given.

9.1.5. Concomitant Medications

9.1.5.1. Steroids

Corticosteroids should be used at the lowest dose to control symptoms of edema and mass effect, and discontinued, if possible. Use of corticosteroids should be recorded in the electronic research database (see Section 16.5). Every effort should be made to keep the dose of steroids at or lower than an equivalent of 4 mg daily of dexamethasone.

9.1.5.2. Anticonvulsants

Anticonvulsants drugs should be used or continued, if indicated. Use of such anticonvulsants should be recorded in the electronic research database.

9.1.5.3. Growth Factors

Routine use of growth factors (i.e. G-CSF, GM-CSF, and erythropoietin) is not permitted. However, therapeutic use of G-CSF in patients with serious neutropenic conditions, such as sepsis, may be used at the investigator's discretion. Use of such growth factors should be recorded in the electronic research database (see Section 16.5).

9.1.5.4. Anti-emetics

The use of anti-emetics will be at the investigator's discretion. Use of anti-emetics should be recorded in the electronic research database (see Section 16.5).

9.1.5.5. Proton Pump Inhibitors

The use of proton pump inhibitors (PPI) (e.g. rabeprazole, omeprazole, pantoprazole, lansoprazole or esomeprazole) is allowed on this study and should be recorded in the electronic research database (see Section 16.5).

9.1.5.6. Pneumocystis jiroveci pneumonia (PJP) prophylaxis

The use of medication (i.e., Bactrim) for PJP prophylaxis in patients on chronic steroids is recommended, but is at the investigator's discretion.

9.1.5.7. Neurosurgical Procedures

If a neurosurgical procedure is required for a reason other than tumor progression (i.e., the onset of hydrocephalus), these procedures should be documented, but will not constitute criteria for declaring the patient "off therapy."

9.1.6. Study Drug Blinding

Not applicable.

9.1.7. Randomization

As of 03/19/2021, randomization was removed from the study when a control arm without neoadjuvant nivolumab and ipilimumab was removed from the study design. See details in Section 15.1.

9.2. Rationale for Selection of Dose, Regimen, and Treatment Duration

Both nivolumab and ipilimumab will be dosed at the FDA recommended dosing levels of 3 mg/kg and 1 mg/kg for combination therapy, respectively. Nivolumab and ipilimumab infusions will occur in the neoadjuvant setting, prior to surgery, with the expectation that neoadjuvant dosing will result in a more robust immune response than adjuvant dosing, as was seen in a study in GBM patients [16].

9.3. Rationale for Correlative Studies

Due to the nature of their activity, checkpoint inhibitors like nivolumab and ipilimumab inherently alter the activity of the immune system. Inhibition of CTLA-4 and PD-1 on T cells using monoclonal antibodies (like ipilimumab and nivolumab) results in increased T-cell proliferation [17], and could serve as a surrogate marker

for therapeutic efficacy. It is important, therefore, to understand how T cells, both in the periphery and intratumoral, are affected by ipilimumab and nivolumab. In a study involving neoadjuvant administration of pembrolizumab in patients with recurrent GBM, tumor interferon-γ-related gene expression was altered by neoadjuvant immunotherapy (Figure 3). Neoadjuvant treatment with pembrolizumab resulted in increased gene expression in a panel of 16 genes related to interferon-γ expression for 9/14 tumors. Markedly, tumors that did not receive neoadjuvant pembrolizumab showed decreased gene expression for 10/14 tumors.

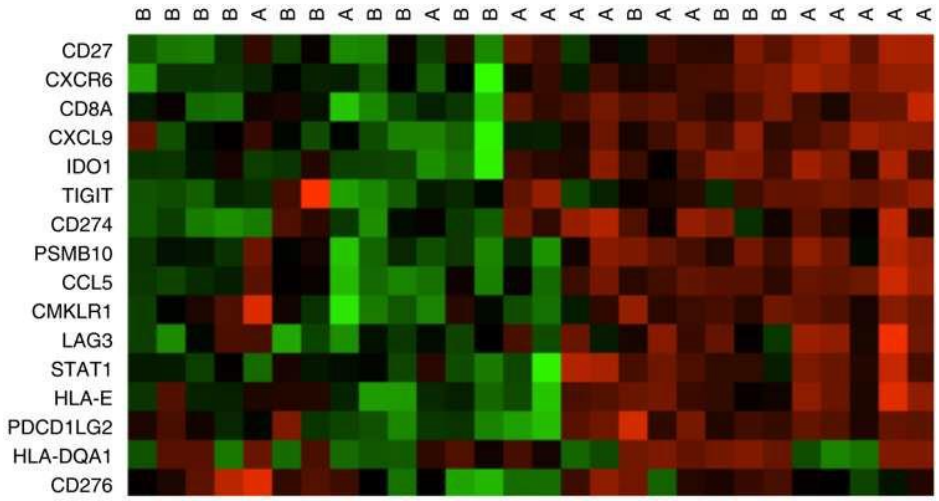


Figure 3: Neoadjuvant immunotherapy alters intratumoral interferon-γ-related gene expression. The letter 'A' represents a tumor treated in the neoadjuvant setting. The letter 'B' represents a tumor treated in the adjuvant setting. The majority (10/14) of patients treated with adjuvant pembrolizumab had tumors with decreased levels of mRNA expression. Conversely the majority (9/14) of patients treated with neoadjuvant pembrolizumab had tumors with increased levels of mRNA expression. Adapted from Cloughesy et. al.

Immune correlative studies will also aid in understanding, which patients respond better to checkpoint inhibition for future studies. For these purposes, blood will be drawn at various time points throughout the study, as outlined in Table 1.

Additionally, a sample of the resected tumor will be requested for correlative analysis if enough tissue is available after standard pathologic testing. We will also request a sample of archival tissuefrom an extracranial site pretreatment. The full correlative study plan is detailed in Section 12.7.5 and the Correlative Lab Manual (CLM).

9.4. Definition of Evaluable Subjects, On Study, and End of Study

Section 15.2 indirectly addresses the definition of evaluable patients. All eligible patients who initiate checkpoint treatment will be followed for survival regardless of compliance to assigned treatment. In addition, all patients who initiate checkpoint treatment will be included in the denominator for assessing feasibility, whether or not a surgery occurs.

Participants will be considered on study once they have signed the informed consent form and eligibility has been confirmed. The study will be ended once all subjects have completed follow up and all data analysis is complete.

9.5. Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 12.6, which describes procedures and process for prematurely withdrawn patients.

10. STUDY DRUG

10.1. Nivolumab (Opdivo®)

10.1.1. Names, Classification, and Mechanism of Action

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa [18].

T-cell proliferation and cytokine production are inhibited by the binding of PD-1 to its ligands, PD-L1 and PD-L2. Some tumors upregulate the PD-1 ligands which contributes to reduced T-cell immune response and surveillance in tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth [18].

10.1.2. Packaging and Labeling

Nivolumab is packaged in a clear glass vial with a grey rubber top (100 mg/mL) or a purple rubber top (40 mg/mL).

The label includes the following:
NDC number
“Rx only”
Concentration of solution
“For Intravenous Infusion Only
Single-Dose Vial; Discard Unused Portion”

The label will also include the following statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”

10.1.3. Supply, Receipt, and Storage

Nivolumab is supplied as a clear to opalescent, colorless to pale-yellow solution in a single dose vial of either 100 mg/mL or 40 mg/mL. The vial should be discarded if the solution appears cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinacious particles. Nivolumab will be shipped directly from BMS to ICS on ice and should be stored at 2-8°C, protected from heat and light, upon receipt. Do not freeze or shake.

10.1.4. Dispensing and Preparation

Nivolumab is given via IV over 30-60 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). The drug product should be visually inspected for particulate matter and discoloration prior to administration and infusion preparation. If the vial of solution appears cloudy, is discolored, or

contains extraneous particulate matter other than a few translucent-to-white, proteinacious particles, it should be discarded[18]. Do not shake the vial.

The infusion solution should be prepared as follows [18]:

- Withdraw the required volume of nivolumab from the vial and transfer into an intravenous container.
- Dilute nivolumab 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 or empty vials of nivolumab.

The infusion should be administered immediately once prepared. If the diluted nivolumab infusion solution is not used immediately, the solution can be stored at room temperature for up to 4 hours from the time of preparation (including storage of the infusion in the IV container and infusion time) or at 2-8°C for up to 24 hours from the time of preparation [18].

10.1.5. Disposal and Destruction

All empty vials and used IV bags of nivolumab should be disposed of based on pharmacy guidelines.

10.2. Ipilimumab (Yervoy®)

10.2.1. Names, Classification, and Mechanism of Action

Ipilimumab is a recombinant, human monoclonal IgG1 kappa immunoglobulin that binds to CTLA-4. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CLTA-4 and blocks the interaction with its ligands, CD80/CD86. CTLA-4 blockade has been shown augment the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor response [19].

10.2.2. Packaging and Labeling

Ipilimumab is packaged in a clear glass vial with a purple rubber top with a red label (200 mg/40 mL) or a teal rubber top with a yellow label (50 mg/ 10mL).

The label includes the following:
NDC number
“Rx only”
Concentration of solution
“For Intravenous Infusion Only
Single-Dose Vial; Discard Unused Portion”

The label will also include the following statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”

10.2.3. Supply, Receipt, and Storage

Ipilimumab is supplied as a clear to slightly opalescent, colorless to pale-yellow solution in a single dose vial of either 50 mg/10 mL or 200 mg/40 mL. The vial should be discarded if the solution appears cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles. Ipilimumab will be shipped directly from BMS to ICS on ice and should be stored at 2-8°C, protected from heat and light, in the original carton, upon receipt. Do not freeze or shake.

10.2.4. Dispensing and Preparation

Ipilimumab is given via IV over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter. The drug product should be visually inspected for particulate matter and discoloration prior to administration and infusion preparation. If the vial of solution appears cloudy, is discolored, or contains foreign particulate matter other than a few translucent-to-white, amorphous particles, it should be discarded [19].

The infusion solution should be prepared as follows [19]:

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of ipilimumab.

The prepared solution should be administered as follows [19]:

- Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

10.2.5. Disposal and Destruction

All empty vials and used IV bags of ipilimumab should be disposed of based on pharmacy guidelines.

11. SUBJECT ELIGIBILITY

11.1. Inclusion Criteria

1. Patients must have at least 1 previously untreated, solid tumor brain metastasis that is ≤4 cm in the largest dimension that is planned for standard of care surgical resection. Metastasis must be planned for treatment with post-surgical SRS per standard of care. Primary tumor histology must be one of the following:
    - Squamous NSCLC
    - Non-squamous NSCLC without known ALK, EGFR, and ROS mutation
    - RCC
    - Urothelial carcinoma
    - Ovarian carcinoma
    - Melanoma
    - Triple negative breast cancer that is PD-L1 positive
    - Other solid tumor histologies may be eligible at the discretion of the PI if they are known to respond to immunotherapy containing regimens.
2. Patient must be asymptomatic or minimally symptomatic, requiring the equivalent of ≤ 4 mg dexamethasone daily for at least 7 days prior to enrollment
3. Patient or partner(s) meets one of the following criteria:
    a) Non-childbearing potential (i.e. not sexually active, physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile, or any male who has had a vasectomy). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Postmenopausal for purposes of this study is defined as 1 year without menses.; or
    b) Childbearing potential and agrees to use one of the following methods of birth control: approved hormonal contraceptives (e.g. birth control pills, patches, implants, or infusions), an intrauterine device, or a barrier method of contraception (e.g. a condom or diaphragm) used with spermicide.
4. Age ≥ 18 years of age at the time of entry into the study
5. Karnofsky Performance Score (KPS) ≥ 70
6. Prothrombin and Partial Thromboplastin Times ≤ 1.2 x normal at screening
7. Neutrophil count ≥ 1000 at screening
8. Hemoglobin ≥ 9 g/dl at screening
9. Platelet count ≥ 100,000/µl unsupported is necessary at screening
10. Creatinine ≤ 1.5 x ULN at screening
11. A signed informed consent form approved by the Institutional Review Board (IRB) will be required for patient enrollment into the study. Patients must be able to read and understand the informed consent document and must sign the informed consent indicating that they are aware of the investigational nature of this study
12. Ability to undergo MRI

11.2. Exclusion Criteria

1. Females who are pregnant or breast-feeding
2. Patients with an impending, life-threatening cerebral herniation syndrome, based on the assessment of the study neurosurgeons or their designate
3. Patients with severe, active co-morbidity, defined as follow:

a) Patients with an active infection requiring intravenous treatment or having an unexplained febrile illness (Tmax > 99.5°F/37.5°C)
b) Patients with known immunosuppressive disease or known uncontrolled human immunodeficiency virus infection
c) Patients with unstable or severe intercurrent medical conditions such as severe heart disease (New York Heart Association Class 3 or 4)

4. Patients who have not recovered from the toxic effects of prior chemo- and/or radiation therapy.
5. Patients must not have received immunotherapy within 3 months prior to enrollment
6. Patients with prior, unrelated malignancy requiring current active treatment in the last 3 years with the exception of cervical carcinoma *in situ* and adequately treated basal cell or squamous cell carcinoma of the skin
7. Patients with a known history of hypersensitivity to nivolumab, or any components of nivolumab
8. Patients with a known history of hypersensitivity to ipilimumab, or any components of ipilimumab
9. Patients with active autoimmune disease requiring systemic immunomodulatory treatment within the past 3 months.
10. History and/or confirmed pneumonitis, or extensive bilateral lung disease on high resolution/spiral CT scan.

12. SCREENING AND ON-STUDY TESTS AND PROCEDURES

Table 1: Schedule of Study Tests and Procedures

Description	Screening	Treatment Period				
	Up to 14 days prior to surgical resection	Neoadjuvant IO	Surgery		Adjuvant SRS[1]	Follow-up
Week[2]		-1	1	3[3]	4	7, 13 +SOC visits
Day[2]		-10 to -4	1	15	22 (± 3 weeks)	29 + SOC visits
General Evaluations						
Informed Consent	X					
Physical Exam[4]	X	X	X	X		X
Neurologic Exam[4]	X	X	X	X		X
Performance Status[4]	X	X	X	X		X
Adverse Events		Continuous[5]				
Laboratory Evaluations						
CBC w/diff	X	X[6]	X	X		X
CMP	X	X[6]	X	X		X
Thyroid panel	X					X
PT, aPTT	X					
Pregnancy test[7]	X	X[6]				
Whole blood for correlative analysis (3x10 mL yellow top)[8]	X		X[9]	X	X[10]	X[11]
Archival tissue sample[12]	X					
Surgical tissue sample			X[13]			
Disease Evaluations						
MRI of the brain[14]	X					X[15]
Treatment						
Ipilimumab		X				
Nivolumab		X				
Surgery[16]			X			
SRS					X	

[1] Number of fractions for SRS treatment will be assigned at physician's discretion
[2] Weeks and days listed are approximate.
[3] Post-operative visit
[4] Clinical evaluations will include a general physical examination, complete neurologic examination, and KPS rating.
[5] Adverse events will be continuously monitored after the first study-mandated agent is administered to the patient and reviewed monthly by the study PI. AE collection will cease 100-days after surgery, or 100 days after ipilimumab/nivolumab infusion for patients who do not undergo surgery.
[6] Only drawn if more than 7-days (24-hours for pregnancy) post screening draw
[7] For women of childbearing potential
[8] Whole blood should be sent to the Substrate Services Core (SSCRS) for processing and then sent to Dr. Kent Weinhold's laboratory
[9] Blood should be drawn prior to surgical resection
[10] Blood should be drawn prior to SRS
[11] Drawn only at the week 7 follow-up visit
[12] A sample of archival tissue from the primary or other extracranial tumor will be requested for correlative analysis, if available.
[13] A sample of tissue from the resected metastases will be requested for correlative analysis, if available.
[14] MRI of the brain should be accompanied by systemic staging scans per standard of care. Though not dictated by the protocol, results of standard of scare systemic staging scans should be recorded in the eCRF.
[15] No MRI taken at week 7. Follow-up MRIs will be taken at week 13 (± 2 weeks) and continue every 12 weeks (± 4 weeks) thereafter.
[16] Surgery is performed per SOC.

12.1. Screening Examination

All screening procedures should occur within 14 days prior to the planned surgical resection. An informed consent form must be signed by the patient prior to initiating any screening tests or procedures. Screening test and procedures include a physical exam, neurological exam, performance (KPS) status, a pregnancy test, and blood tests. Blood for immune monitoring will also be collected during screening. An archival tissue sample from the primary tumor will be requested for correlative analysis, if available.

If a subject does not receive nivolumab or ipilimumab, minimal records regarding the subject will be retained in the study database. Participants who screen fail after providing informed consent but before receiving study-related treatment will be withdrawn, and these subjects will be excluded from all analyses.

12.2. Treatment Period

Day -10 to -4:

- Physical exam, neurological exam, and KPS
- Laboratory testing including:
    - CBC with differential
    - CMP
    - Beta-HCG, if appropriate and > 24 hours post screening Beta-HCG
- Ipilimumab infusion
- Nivolumab infusion

Day 1 (prior to surgery):

- Physical exam, neurological exam, and KPS
- Laboratory testing including:
    - CBC with differential
    - CMP
    - PT, aPTT
- Whole blood (3 x 8.5 mL yellow top tubes) for immune monitoring, collected prior to surgery
- Surgical resection

Week 3 (± 1 week), surgical follow-up visit:

- Physical exam, neurological exam, and KPS
- Laboratory testing including:
    - CBC with differential
    - CMP
- Whole blood (3 x 8.5 mL yellow top tubes) for immune monitoring

Week 4 (± 3 weeks):

- Whole blood (3 x 10 mL yellow top tubes) for immune monitoring
- SRS treatment (number of fractions given will be at the physician's discretion)

12.3. End of Treatment

Week 7 (±1 week):

- Physical exam, neurological exam, and KPS
- Laboratory testing including:
  - CBC with differential
  - CMP
  - Thyroid panel
- Whole blood (3 x 10 mL yellow top tubes) for immune monitoring

12.4. Follow-up Period

Week 13 (±2 weeks) and at standard of care visits per the treating physician's discretion for up to 18 months:

- Physical exam, neurological exam, and KPS
- Laboratory testing including:
  - CBC with differential
  - CMP
  - Thyroid panel
- MRI of the brain accompanied by any standard of care systemic staging scans. Though standard of care systemic staging scans are not dictated by this protocol, the results of such scans should be included in the eCRF.

12.5. End of Study

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

The study will be considered complete once enrollment has been met, follow-up procedures outlined in Section 12.4 have been conducted on all subjects, and data analysis is concluded. The study may also be terminated early for any reason by the PI.

Subjects that are lost to follow-up will be documented in the patient record and in the 21 CFR Part 11 database. In the compliant database, the subject will be marked as "Patient Status Unknown," along with a corresponding explanation, if any.

12.6. Early Withdrawal of Subject(s)

12.6.1. Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- If, in the investigator's medical judgment, further participation would be injurious to the subject's health or wellbeing
- Protocol deviation
- Administrative issues
- Non-compliance of the subject
- Pregnancy
- They do not receive neoadjuvant nivolumab and ipilimumab infusions

12.6.2. Follow-up Requirements for Early Withdrawal

Subjects should be seen in clinic or contacted at a minimum of every 3 months until 18 months after initiating study treatment, if possible.

12.6.3. Replacement of Early Withdrawal(s)

Subjects who withdraw from the study without receiving both nivolumab and ipilimumab will be considered non-evaluable; those subjects will be replaced.

12.7. Study Assessments

12.7.1. Medical History

Standard medical history will be obtained and documented per institutional guidelines.

12.7.2. Physical Exam

Standard physical exam and neurological assessment will be conducted and documented per institutional and PRTBTC guidelines.

12.7.3. Radiographic Review

Starting at week 13, an MRI of the brain will be obtained at the subsequent standard of care visits outlined in Section 12.4. Given that imaging following immunotherapy differs greatly from what is typically seen following chemoradiation treatment or treatment with anti-angiogenic compounds, evaluation of response using Macdonald criteria or Response Assessment in Neuro-Oncology (RANO) criteria is not appropriate in this trial. Due to differences in the nature of primary brain tumors and brain metastases, a modified version of RANO called RANO-BM will be used.

12.7.4. Laboratory Evaluations

The timing of laboratory assessments that will be obtained during the course of the study is given in Table 1. A list of each evaluation is below.

- CBC with differential

- CMP
- PT, aPTT
- Beta-HCG, if appropriate
- Thyroid panel

12.7.5. Correlative Assessments

Correlative studies will assess and compare the immune response observed within patients treated with neoadjuvant immunotherapy. Inhibition of CTLA-4 and PD-1 on T cells using monoclonal antibodies (like ipilimumab and nivolumab) results in increased T-cell proliferation [17], and could serve as a surrogate marker for therapeutic efficacy. To examine T-cell proliferation rates, Ki67 staining will be performed on PD-1+/CD8+ T cells extracted both from the peripheral blood and from resected tissue (when available). Blood will be drawn longitudinally during treatment (see Table 1 in Section 12) to study how a single dose of nivolumab and ipilimumab before surgery affect T-cell proliferation over time. Assessing how Ki67 levels on peripheral-blood T cells change over time in patients receiving neoadjuvant immunotherapy will provide evidence that neoadjuvant checkpoint inhibition alters T-cell function. Additional immune profiling will be performed to understand how the immune system is responding to neoadjuvant immunotherapy compared to the control group. This immune profiling will be performed with assays including, but not limited to: RNASeq, 28 color flow cytometry, and IHC. These assays may be run on cells from peripheral blood, resected tissue (if available), and archival tissue (if available). Analysis will be performed to correlate peripheral blood immune responses to those within the tumor. An alternative protocol will be established to collect fresh tissue in solid tumor brain metastases patients who are undergoing standard of car resection and not receiving immunotherapy to compare as a control for RNA sequencing and 28 color flow panels. 28 color flow panel analysis will be performed by Dr. Kent Weinhold or his designee.

13. SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

13.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre- existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of nivolumab or ipilimumab, whether or not related to use of nivolumab or ipilimumab. Abnormal laboratory findings that are able to be graded via CTCAE will be collected as AEs and attribution will be reviewed by the PI.

From the time the subject signs the informed consent form until 100-days after surgery, or 100 days after ipilimumab and nivolumab infusion for patients who do not undergo surgery, all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 5. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows, with the study drug specified to be ipilimumab, nivolumab, protocol-mandated surgery, or SRS:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

For additional information on adverse event management algorithms, please see Sections 18.1 and 18.2 for nivolumab and ipilimumab, respectively.

13.1.1. AEs of Special Interest

See Section 9.1.3 for management of anticipated adverse events.

13.1.2. Reporting of AEs

Any AE occurrence (spontaneously volunteered and enquired for, as well as observed AEs) during the study must be documented in the patient's medical records in accordance with the Investigator's normal clinical practice and on the

AE page of the eCRF. SAEs that occur during the study must be documented in the patient's medical record, on the AE eCRF, and on the SAE form.

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

If an abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed as appropriate. In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

A database of all adverse events (not just those considered related to the study drug) will be maintained in a 21 CFR Part 11 compliant database. The event will be categorized by organ system, relationship to treatment, its grade of severity, and resolution. The PI and study statistician will periodically review the collective adverse events with the intention of identifying any trends or patterns in toxicity. If any such trends are identified, depending on their severity and frequency, a protocol amendment will be considered.

13.2. Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Note: Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

13.2.1. Reporting of SAEs

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, should be collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

All SAEs should be reported immediately to the Principal Investigator or designee. Only adverse events that the Principal Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e. more likely than not) related to the research must be reported to the Duke IRB. An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form. Reportable adverse events will be submitted in the electronic IRB system, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious AE that is unanticipated and related or possibly/probably related to study treatment;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the study treatment than unrelated.

The PI-Sponsor must report to the FDA, in an IND safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the PI-Sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction (i.e. there is a reasonable possibility that the drug caused the adverse event)
- Serious
- Unexpected (see nivolumab and/or ipilimumab investigator brochures)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report. The PI-Sponsor is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected adverse reaction). The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other adverse events will be reported to the FDA in the Annual Report.

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. SAEs must be collected that relate to any later protocol-specified procedure (eg, surgery and SRS). SAEs, whether related or not related to study drug, and pregnancies (including in a female partner of a male participant) must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAEs should be reported to BMS using a Medwatch form, must include the BMS protocol number, and should be either emailed or faxed as below.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

13.3. Emergency Unblinding of Investigational Treatment

Not applicable.

13.4. Other Reportable Information

Not applicable.

13.5. Special Warnings and Precautions

Not applicable.

13.6. Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable,

accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 14.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Monitoring

This clinical research study will be monitored both internally by the PI, and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI Protocol Review and Monitoring systems (PRMS) review of this protocol begins with an initial review by the Cancer Protocol Committee (CPC). CPC new protocol review focuses on scientific relevance, study design, adequacy of biostatistical input, protocol prioritization, feasibility of completing the study within a reasonable time frame and risk assessment of the trial. The PI will abide by CPC assessment of the level of risk, which will determine the intensity of subsequent DCI monitoring. CPC also conducts annual scientific progress reviews on protocols that are open to enrollment and focus on protocol prioritization, accrual and scientific progress. These reviews are conducted at the time of IRB annual renewals and documentation of all CPC reviews will be maintained in eIRB/iRIS systems.

A determination for the degree of monitoring conducted by the DCI monitoring team is made at the time of initial CPC approval to commensurate with the type and level of intervention, phase, endpoints, degree of risk, size and complexity of the protocol. A formal, independent monitoring will be conducted by the DCI monitoring team according to the risk level and monitoring plan assigned by the CPC until the study is closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

The DCI monitoring team reviews the adequacy of informed consent, enrollment of eligible patients, implementation of protocol-specified procedures and treatment, adequacy of data collection, and appropriateness of adverse event monitoring and

reporting. The DCI monitoring team presents final monitoring reports to the DCI Safety Oversight Committee (SOC) highlighting safety concerns and unresolved issues. The SOC, at a convened meeting, assigns an overall rating of satisfactory, marginal, or unsatisfactory to reflect the overall quality of data, regulatory, consent, eligibility, study conduct and AE reporting. Corrective action plans (CAPs) are developed, implemented, and evaluated as indicated. The SOC will notify the sponsor-investigator and DUHS IRB when significant safety concerns are identified.

The SOC in concert with DCI monitoring team conducts data and safety monitoring for DUHS sponsor-investigator phase I and II, therapeutic interventional oncology studies that do not have an independent DSMB. These reviews occur at a minimum annually and more frequently for the high risk studies. The SOC safety reviews include review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC, at a convened meeting, assigns a rating of satisfactory when adequate accrual with lack of excessive toxicity is present.

14.2. Audits

The Duke Office of Audit, Risk and Compliance (OARC) may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

14.3. Data Management and Processing

14.3.1. Case Report Forms (CRFs)

The electronic CRF (eCRF) will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the PI, the study coordinator, the data management team, and the clinical trials coordinator are permitted to make entries, changes, or corrections in the eCRF.

An audit trail will be maintained automatically by the electronic CRF management system, Advarra OnCore. Designated personnel will complete user training, as required or appropriate per regulations.

14.3.2. Data Management Procedures and Data Verification

Access to the electronic databases will be managed by the PRTBTC Data Manager.

Completeness of entered data will be checked be the PRTBTC Data Manager or designee, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

14.3.3. Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

15. STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

15.1. Study Design Overview

This randomized phase II trial is conducted among patients with surgically-resectable, solid tumor brain metastases to assess the impact of neoadjuvant nivolumab and ipilimumab administered before surgery and stereotactic radiosurgery on various clinical and biological endpoints.

The study was originally designed as a randomized phase 2 trial in which patients were randomized via a permuted block randomization algorithm using a 1:1 allocation ratio to receive either Arm 1 (with neoadjuvant nivolumab and ipilimumab) or Arm 2 (without neoadjuvant treatment). Unfortunately, the study faced challenges to enrollment due to delays in treatment caused by the randomizing of patients to a control arm. In a Memo to File dated March 4, 2021 that was submitted to the IRB and FDA, we proposed the removal of randomization in favor of a single-arm study in which all patients will receive neoadjuvant immunotherapy prior to their resection and SRS. This change is reflected in the protocol's amendment date 03/19/2021. This change will not affect the primary endpoint of feasibility. Prior to the writing of this Memo to File, 1 patient had been randomized to receive standard of care surgery and SRS without neoadjuvant immunotherapy. This patient, though eligible, will not be part of the analyses described below.

15.2. Analysis Sets

The primary analysis associated with the assessment of feasibility, survival, progression-free survival, and time to intracranial progression will include all eligible patients who receive both nivolumab and ipilimumab.

Correlative analyses may be limited to only those patients who provide adequate specimens for analyses.

15.3. Patient Demographics and Other Baseline Characteristics

Summaries of clinical and socio-demographic characteristics will be generated for all enrolled patients. Categorical descriptors will be summarized using frequency distributions; whereas, interval variables will be summarized using percentiles, as well as means and standard deviations.

15.4. Treatments

A CONSORT diagram will be generated that describes flow of treatment. The diagram will provide information about the number of patients who receive

neoadjuvant treatment, undergo surgery (on schedule, late, or not at all), and receive SRS. Details about the SRS administered will be summarized.

The number of patients who receive treatment after SRS will also be tabulated with some detail about the type of treatment administered. Data about maintenance treatment, including the type of immunotherapy, will also be summarized.

15.5. Primary Objectives

This study has two primary objectives. This includes an assessment of the feasibility of administering ipilimumab and nivolumab before surgery and SRS in patients with solid tumor brain metastases, as well as an assessment of the effect of neoadjuvant treatment on the proliferation of circulating T-cells.

15.5.1. Primary Objective #1: Feasibility (Surgical Delay)

15.5.1.1. Variable

The first primary objective is to demonstrate that neoadjuvant administration of ipilimumab and nivolumab administered to patients with solid tumor brain metastases before surgery and SRS is feasible. Feasibility will be assessed by the proportion of patients who have their surgery delayed or surgery never occurs as a direct or indirect result of ipilimumab and/or nivolumab treatment. With the checkpoint inhibitors being administered on Day -7, the surgery is scheduled for Week 1, Day 1 (± 3 days). *Surgery will be considered delayed if it never occurs or occurs after Day 4 (i.e. Day 1 + 3)*.

15.5.1.2. Continuous Monitoring of Feasibility and Analysis

The proportion of patients experiencing surgical delay as defined in Section 15.5.1.1 will be computed as the number of patients with delayed surgery or whom never have surgery as a direct or indirect result of ipilimumab and/or nivolumab treatment divided by the total number of patients.

Neoadjuvant treatment patients who have delayed surgery or no surgery due to reasons unrelated to ipilimumab and/or nivolumab treatment will be excluded from the assessment of feasibility. However, this patient will be included in all other analyses if data is available. Reasons for such exclusions will be tabulated. All other patients will be considered evaluable for the assessment of feasibility.

Methods developed for continuous monitoring of toxicity will assess whether the number of surgical delays is not excessive. Based upon the Pocock boundary, the following monitoring rules were developed assuming that a true surgical delay rate of 10% is acceptable, and a surgical delay rate of 20% is too high. Accrual of patients will be suspended if the following conditions are satisfied:

# of Patients Enrolled to Date	Suspend Treatment Assignment if
1 – 4	# Evaluable Patients with Delayed Surgery > 1
5 – 8	# Evaluable Patients with Delayed Surgery > 2
6 – 14	# Evaluable Patients with Delayed Surgery > 3
15+	# Evaluable Patients with Delayed Surgery > 4

These monitoring rules were generated using the R software package. Specifically, the toxbdry function in the clinfun package (https://cran.r-project.org/web/packages/clinfun/clinfun.pdf) that implements methods developed by Jennison and Turnbull [20] and Ivanova et al [21] was used.

If accrual is suspended, the reasons for delay will be carefully reviewed to determine whether accrual to should continue without any protocol modification, be permanently terminated, or whether modifications to the treatment regimen (e.g., removal of ipilimumab from the treatment regimen) should occur.

15.5.1.3. Adverse Events

In addition to feasibility, we will also be monitoring the study for adverse events, both before, during, and after surgery.

Aggregate summaries of adverse events will be generated periodically for study team use, for review by the Safety Oversight Committee, and for submission to ClinicalTrials.gov. Included with these summaries will be a list of all patients experiencing serious adverse events.

Two tabulations will be generated--one that includes all toxicities regardless of attribution, and another that includes only toxicities that are possibly, probably, and definitely related to treatment. For each of these tabulations, the maximum grade (according to CTCAE version 5) of each type of toxicity experienced by each patient will be summarized with frequency distributions. These tabulations will also summarize adverse events by step in the treatment regimen (e.g. neoadjuvant treatment period, surgery / SRS).

For ClinicalTrials.gov, serious adverse events and other adverse events will be summarized separately. These tabulations will reflect the number of patients who experience each type of toxicity regardless of grade or attribution.

As noted in section 15.5.1.2, if the percentage of patients with surgical delay due as a direct or indirect result of ipilumumab and/or nivolumab treatment is elevated, consideration will be given to modifying the immunotherapy treatment regimen. In addition, if the prevalence of adverse events possibly, probably, or definitely related to combination immunotherapy is higher than

anticipated based upon prior experience with this combination, consideration will also be given to modifying the immunotherapy regimen.

15.5.2. Primary Objective #2: Proliferation of Circulating T-Cells

The second primary objective involves an assessment of whether neoadjuvant immunotherapy will increase proliferation of circulating T-cells compared to baseline measurements.

15.5.2.1. Variable

To examine T-cell proliferation rates, Ki67 staining will be performed on PD-1+/CD8+ T cells extracted both from the peripheral blood and from resected tissue.

As described in Table 1 of Section 12, blood will be drawn longitudinally during treatment to study how a single dose of nivolumab and ipilimumab before surgery affect T-cell proliferation over time.

The primary outcome is the fold-change in Ki67 levels on peripheral-blood T cells between baseline and Day 1.

15.5.2.2. Statistical Hypothesis, Model, and Method of Analysis

As noted in Section 15.5.2.1, the primary outcome for each patient is the fold- change in Ki67 levels between baseline and Day 1. The mean fold-change will be tested using a one-sample t-test. If assumptions for conducting a t-test are violated, a logarithmic transformation may be considered as well as a Wilcoxon one-sample test.

15.5.2.3. Additional Analyses

Ki67 from circulating PD-1/CD8+ T cells at Day 1 will be correlated to intratumoral PD-1/CD8+ T cells based on nonparametric correlation, Spearman's rank order correlation.

15.6. Exploratory Objectives

This study has several exploratory objectives including the description of survival, time to local intracranial progression, time to distant intracranial progression, time to overall intracranial progression, and progression-free survival. The rate of radionecrosis will also be explored, as immune expression profiles.

Some of the proposed exploratory analyses may generate p-values. If they do, they will be viewed as descriptive and exploratory in nature.

15.6.1. Exploratory Objective #1: Survival

Survival is defined as the time between initiation of checkpoint treatment and death; survival time will be censored if the patient remained alive at the time of last follow-up. A Kaplan-Meier estimator will describe the survival of patients and associated survival statistics (e.g. median survival, survival at 6 months, 12 months, and 18 months) will be estimated.

In addition, exploratory analyses will assess the impact of fold-change in T-cell proliferation (KI-67) between baseline and Day 1 on subsequent survival, using a Cox model with fold-change as predictors of survival post-surgery.

15.6.2. Exploratory Objectives #2 - #5: Disease Progression

Several different efficacy measures of progression will be computed as part of exploratory objectives #2 - #5:

- The time to local intracranial progression is the time between initiation of checkpoint treatment and first identification of local intracranial progression, which is defined by RANO-BM criteria. If a patient experiences a distant intracranial progression or dies before documentation of local progression, the time to local intracranial progression will be censored at the time of distant intracranial progression or the time of death.

- The time to distant intracranial progression is the time between initiation of checkpoint treatment and first identification of distant intracranial progression, which is defined by RANO-BM disease progression criteria. If a patient locally progresses intracranially or dies before documentation of distant intracranial progression, the time to distant intracranial progression will be censored at the time of local intracranial progression or the time of death.

- The time to overall intracranial progression is the time between initiation of checkpoint treatment and first identification of intracranial progression (distant or local), as defined by RANO-BM criteria. If a patient dies before documentation of intracranial progression, the time to overall intracranial progression will be censored at the time of death.

- Progression-free survival is the time between initiation of checkpoint treatment and first progression (intracranial or extracranial), or death if the patient dies without documented disease progression, as defined by RECIST 1.1. If the patient remains alive without disease progression at the time of analysis, progression-free survival will be censored at the time of last follow-up.

Given that death, local intracranial recurrence, and distant intracranial recurrence are competing events, time to local intracranial recurrence, time to distant intracranial recurrence, and time to overall intracranial recurrence will be graphically described using a cumulative incidence function.

15.6.3. Exploratory Objectives #6: Radionecrosis

Rates of radionecrosis will also be determined based on radiographic and clinical suspicion or tissue confirmation when available. The proportion of patients who experience radionecrosis will be estimated with confidence intervals in the two treatment groups.

15.6.4. Exploratory Objectives #7: Immune Expression Profiles

Various exploratory analyses will be conducted to describe the immune expression profiles of patients. As noted previously immune profile assays may be run on cells from peripheral blood, resected tissue, and archival tissue using RNASeq, 28 color flow cytometry, IHC, and other methods. Some analyses may not be pre-specified, and may be motivated by other study findings or the evolving clinical literature that is available at the time accrual has been completed.

Nanostring expression data will be normalized as per system guidelines. Exploratory analysis of highly differentially expressed genes will be utilized in assessing association to Ki67 from circulating PD-1/CD8+ T cells and to intratumoral PD- 1/CD8+ T cells. Additionally, differentially expressed genes will be incorporated in exploratory models of survival outcomes.

15.7. Interim Analysis

No interim efficacy analyses will be performed. However, continuous monitoring of surgical timing/delay will occur as described in Section 15.5.1.2.

15.8. Sample Size Calculation

Twenty (2) patients will be enrolled onto this study and treated with ipilimumab and nivolumab. We anticipate that due to drop-out and/or sample quality issues Ki67 data will be available from approximately 17 patients.

Kim et al (2019) [23] reports that a higher fold-change in the percentage of Ki-67+ cells among PD1+ CD8+ T cells 7 days after the first dose of anti-PD-1 therapy is associated with greater efficacy. The distribution of this fold-change is graphically presented in Figure 2A of the Kim article. Based upon a crude estimate of the value of KI-67 associated with each data point in this figure, mean fold-changes were computed. The mean fold- change among the 11 patients with durable clinical response is 4.9 (SD=2.0; CV = 0.42); whereas the mean fold-change among the 20 patients with non-durable response is 2.5 (SD=1.3; CV=0.54). Overall, the mean fold-change is 3.4 (SD=2.0; CV=0.6).

Assuming that CV=0.6, a one-sample t-test (α=0.05; two-tailed) has >95% power to detect a mean fold- change of 1.7 among the 17 patients with evaluable Ki67 data.

16. ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

16.1. Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

16.2. DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

16.3. Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

16.4. Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches,

photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (eCRF) will be the primary data collection document for the study. The eCRFs will be updated within two weeks of acquisition of new source data. Only approved study staff (See Section 14.3.1) are permitted to make entries, changes, or corrections in the CRF. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system, Medidata Rave.

16.5. Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Clinical Research Unit.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database, Medidata Rave, which is housed in an encrypted and password-protected file on a secure network drive. Access to electronic databases will be managed by the PRTBTC Data Manager. Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

16.6. Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 13 (Section 13.6 in particular) and Section 14.

16.7. Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

16.8. Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA (if an IND is involved)
- at least two years after formal withdrawal of the IND associated with this protocol (if an IND is involved)
- at least six years after study completion (Duke policy)

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18. APPENDICES

18.1. Nivolumab Safety Algorithms

Table 2: GI Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/Colitis	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately **If worsens:** • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	**If improves to grade 1:** • Resume I-O therapy per protocol **If persists > 5-7 days or recur:** • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. **If worsens or persists > 3-5 days with oral steroids:** • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	**If improves:** • Continue steroids until grade 1, then taper over at least 1 month **If persists > 3-5 days, or recurs after improvement:** • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Table 3: Renal Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	**If returns to baseline:** • Resume routine creatinine monitoring per protocol **If worsens:** • Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	**If returns to grade 1:** • Taber steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol **If elevations persists > 7 days or worsen:** • Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	**If returns to grade 1:** • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Table 4: Pulmonary Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3-4
Grade 2-3 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days **If improves:** • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** • Treat as Grade 3-4
Grade 4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	**If improves to baseline:** • Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** • Add additional immunosupression

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

Table 5: Hepatic Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	**If returns to baseline:** • Resume routine monitoring, resume I-O therapy per protocol **If elevation persists > 5-7 days or worsens:** • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULT or T. bili >3 x ULN	• Discontinue I-O therapy per protocol* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	**If returns to Grade 2:** • Taper steroids over at least 1 month **If does not improve in >3-5 days, worsens or rebounds:** • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Table 6: Endocrinopathy Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

Asymptomatic TSH Elevation	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	• Evaluate endocrine function • Consider pituitary scan **Symptomatic with abnormal lab/pituitary scan:** • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent • Initiate appropriate hormone therapy **No abnormal lab/pituitary MRI scan but symptoms persist:** • Repeat labs in 1-3 weeks / MRI in 1 month	**If improves (with or without hormone replacement):** • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

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

Table 7: Skin Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash	Management	Follow-up
Grade 1-2 Covering ≤ 30% BSA*	• Symptomatic therapy (e.g., antihistamines, topical steroids) • Continue I-O therapy per protocol	**If persists > 1-2 weeks or recurs:** • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol **If worsens:** • Treat as Grade 3-4
Grade 3-4 Covering > 30% BSA; Life threatening consequences *^	• Delay or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent	**If improves to Grade 1:** • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Table 8: Neurological Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	• Continue to monitor the patient **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	**If improves to baseline:** • Resume I-O therapy per protocol when improved to baseline **If worsens:** • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** • Taper steroids over at least 1 month **If worsens or atypical presentation:** • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Table 9: Myocarditics Adverse Event Management Algorithm.

Grade of Myocarditis	Management	Follow-up

Grade 2
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

18.2. Ipilimumab Safety Algorithms

Table 10: GI Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue ipilimumab. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/Colitis	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue ipilimumab • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Withold/delay ipilimumab • Symptomatic treatment	**Symptoms improve/resolve (grade 0/1):** • Resume ipilimumab **Symptoms persists > 5-7 days, worsen, or recur:** • Moderate to high dose steroids PO (e.g., prednisone 0.5-1.0 mg/kg/day) • Continue to hold/delay ipilimumab until grade 1 • When symptoms are grade 1 or less, slowly taper steroids over at least 1 month and resume ipilimumab **Symptoms worsen:** • Treat as grade 3/4
Grade 3-4 Diarrhea (G3*): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3*): fever, ileus, peritoneal signs	• Permanently discontinue ipilimumab • High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone) • Consider endoscopy	**Symptoms improve:** • Continue steroids (same dose) until grade 1 • Then taper over at least 1 month **Symptoms persist 3-5 days, or recur after improvement:** • 1 dose* infliximab 5 mg/kg (if no contraindication)

*G4: life-threatening, perforation *Some patients have required a second dose of infliximab

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

Table 11: Hepatic Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation	Management	Follow-up
Grade 1 AST or ALT ≤ 2.5 x ULN Or Total bilirubin ≤ 1.5 x ULN	• Continue ipilimumab	• Continue LFT monitoring prior to each dose
Grade 2 AST or ALT > 2.5 to ≤ 5 x ULN or Total bilirubin > 1.5 to ≤ 3 x ULN	• Increase frequency of monitoring (q3d) • Withhold/delay ipilimumab while investigating alternative etiology	**Return to baseline:** • Resume q3w monitoring • Resume ipilimumab **Elevations persist > 5-7 days or worsen, and no alternative etiologies are identified:** • Consider moderate to high dose steroids PO (e.g., 0.5-1 mg/kg/day prednisone or equivalent)
Grade 3-4 AST or ALT > 5 x ULN or Total bilirubin > 3 x ULN	• Discontinue ipilimumab* • Increase frequency of monitoring (q1-3d) • High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone**)	**AST/ALT/Tbili returns to Grade 2:** • Taper steroids over at least 1 month **Labs do not decrease over 3-5 days, worsen or rebound:** • Add mycophenolate mofetil 1 g BID • If no response within 3-5 days, consider other immunosuppressants per local guidelines

*Ipilimumab may be held/delayed rather than discontinued if AST/ALT ≤ 8 X ULN and Tbili < 5 X ULN. Resume ipilimumab when AST/ALT/Tbili return to grade 2 and meet protocol specific retreatment criteria.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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

Table 12: Endocrinopathy Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

<table>
<tr><td>Asymptomatic TSH Elevation</td><td colspan="2">• Continue ipilimumab
• If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult</td></tr>
<tr><td>Symptomatic endocrinopathy</td><td>• Evaluate endocrine function
• Consider pituitary scan
Symptomatic with abnormal lab/pituitary scan:
• Withhold/delay ipilimumab
• High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone)
• Initiate appropriate hormone therapy
No abnormal lab/pituitary scan but symptoms persist:
• Repeat labs in 1-3 weeks / MRI in 1 month</td><td>Symptoms resolve (with or without hormone replacement):
• Taper steroids over at least 1 month
• Resume ipilimumab
• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component</td></tr>
<tr><td>Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)</td><td>• Rule out sepsis
• Stress dose of IV steroids with mineralocorticoid activity
• IV fluids
• Consult endocrinologist
• If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy</td><td></td></tr>
</table>

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

Table 13: Skin Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab.

Grade of Rash	Management	Follow-up
Grade 1-2	• Symptomatic therapy (e.g., antihistamines, topical steroids) • Continue ipilimumab	**Symptoms resolve:** continue ipilimumab **If persists > 1-2 weeks or recurs:** • Continue ipilimumab • Moderate to high dose steroids PO (e.g., 0.5-1.0 mg/kg/day lprednisone) • Once controlled, taper steroids over at least 1 month
Grade 3-4	• Hold/delay ipilimumab (regardless of relationship) • Take photos of rash • Consider skin biopsy • Dermatology consult • High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone)	**Symptoms resolve / return to Grade 1:** • Taper steroids over at least 1 month • Resume ipilimumab • Discontinue if grade 4 toxicity considered related

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

Table 14: Neurological Adverse Event Management Algorithm. Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab. Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.

Severity of Neurological Toxicity	Management	Follow-up
Grade 1	• Continue ipilimumab	• Continue to monitor the patient. If symptoms worsen, treat as below
Grade 2	• Hold/delay ipilimumab • Treat symptoms per local guidelines	• Resume ipilimumab when resolved/grade 1. If symptoms worsen, treat as below.
Grade 3-4 sensory	• Discontinue ipilimumab if considered related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone)	**Symptoms resolve / return to Grade 2:** • Taper steroids over at least 1 month
Grade 3-4 motor	• Discontinue ipilimumab regardless of relationship • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/day methylprednisolone)	**Symptoms resolve / return to Grade 2:** • Taper steroids over at least 1 month **Symptoms do not resolve or progress; atypical presentation:** • Consider IVIg or other immunosuppressive therapies per local guidelines

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