Title: **An Open Label, Randomized Study of Neoadjuvant Nivolumab and Chemotherapy, With or Without Sub-ablative Stereotactic Body Radiation Therapy, for Resectable Stage IIA to IIIB Non-small Cell Lung Cancer**

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SCHEMA

1.0 OBJECTIVES

1.1 Primary Objective

- To compare the complete pathological response rate after 3 cycles of neoadjuvant nivolumab and platinum-based doublet chemotherapy vs. the same regimen with the addition of sub-ablative stereotactic radiation therapy (8 Gy x 3) directed at the primary lung tumor.

1.2 Secondary Objectives

- To characterize the rate of Major Pathological Response (MPR), defined as ≤ 10% residual viable tumor cells at the time of surgical resection in the primary tumor and lymph nodes, as assessed by local pathology laboratory.
- To characterize rates of Event Free Survival (EFS), defined as survival without documented disease progression per RECIST v1.1 that precludes surgery for local or distant disease recurrence.

1.3 Exploratory Objectives

- To characterize the rate of pathological downstaging of biopsy confirmed positive lymph nodes not in the SBRT field.
- To characterize rates of Disease-Free Survival (DFS), defined as survival without local or distant recurrence or occurrence of new primary NSCLC.
- To characterize rates of Overall Survival (OS) after study enrollment.
- To characterize the incidence of adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- To describe surgical safety and the incidence and severity of surgery-related adverse events.

- To characterize rates of clearance of ctDNA following neoadjuvant therapy and definitive surgical treatment
- To evaluate whole tumor RNAseq from pre- and post- treatment tissue samples to assess for predictors and signatures of pathologic response.
- To evaluate gene expression in pre- and post-treatment blood samples to assess for predictors and signatures of complete pathologic response.
- To assess the expression characteristics of PD-L1, infiltrating immune cells and TMB, and their association with clinical outcomes.

1.4 Rationale and Hypothesis

Approximately 40% of the 235,000 patients diagnosed with NSCLC in the United States will have early-stage disease (stages I-IIIA)[1]. Although surgical resection is the treatment of choice, five-year overall survival is only 55% and disease-free survival (DFS) maybe as low as 40% at five years[1,2]. Several randomized trials have shown an improvement in patient survival with the addition of neoadjuvant or adjuvant chemotherapy to surgery. A meta-analysis of all randomized trials confirmed these results and showed that the absolute improvement in 5-year survival after neoadjuvant or adjuvant chemotherapy is only 5% [3,4]. Despite this statistically significant improvement in survival, 36-50% of patients still develop locally recurrent or metastatic disease[2,5,6]. As such, efforts have been made to move targeted therapy and immunotherapy, drugs with notable success in the stage IV setting, into earlier stage disease. Although previous large international adjuvant trials testing the efficacy of targeted therapies and tumor vaccines failed[7-9], recent trials have shown improvements in DFS using adjuvant EGFR targeted therapy or immunotherapy[10,11]. However, given the low rates of uptake and completion of adjuvant therapy in clinical trials and in the real-world setting, it is suggested by many that neoadjuvant therapy may be the preferred strategy for patients with locally advanced disease. This is particularly true of neoadjuvant immunotherapy, which offers several advantages over an adjuvant strategy: (1) therapy can be given and a T cell response generated against in situ primary tumor with a diverse antigen load; (2) the patient's immune system remains largely intact; (3) neoadjuvant therapy may be better tolerated than adjuvant

therapy after lung resection; and finally (4) pathologic response can be used to determine treatment efficacy and potentially allow for changes of therapy. Given these potential advantages, several single arm trials have been undertaken and since published demonstrating the efficacy and safety of neoadjuvant immunotherapy approaches, either alone or in combination with chemotherapy[12-16]. The majority of these trials have targeted the PD1/PD-L1 pathway.

1.4.1 Targeting PD-L1 is a safe and promising strategy in the neoadjuvant setting.
Clinical trials testing antibodies targeting the PD1/PD-L1 pathway have revolutionized the treatment of patients with advanced NSCLC. Treatment with these drugs resulted in clinical response rates in approximately 15-25% of patients with advanced chemo-refractory NSCLC and 20-30% in the first-line NSCLC setting[17-24]. Responses occurred in patients with either squamous or non-squamous cancers. Although responses were more frequently seen in patients whose tumors expressed PD-L1, responses were also observed in patients with PD-L1 negative tumors. Unlike patients treated by chemotherapy or targeted agents, responses achieved by targeting these inhibitory checkpoints were durable in over 80% of responders and occasionally response was maintained even after drug discontinuation. The favorable safety profile and impressive response rates of these antibodies in advanced disease strongly justify evaluation of their efficacy in patients with early stage disease. Recent trials have shown that neoadjuvant anti-PD1 and anti-PD-L1 therapy in early stage NSCLC is safe and well tolerated[12-16]. These trials have shown a high rate of major and complete pathological response rates (20-45%), perhaps better than would have been anticipated from trials of immune-check point inhibitors (ICIs) in advanced disease. Nivolumab, in particular, either alone or in combination strategies, has been used successfully in the neoadjuvant setting. MPR rates have been reported to range from 17-45% for nivolumab alone while CPR rates range from 9-15% [12,16]. This is similar to pathologic response rates to other ICIs used in the neoadjuvant setting. However, when nivolumab was combined with chemotherapy in the neoadjuvant setting, MPR and CPR rates were reported to be as high as 83% and 63% respectively in the single arm NADIM trial[13]. However, the more recently presented (and not yet published) data from the phase 3 CheckMate-816 trial reported a 36.9% MPR and 24% CPR rate in patients treated with neoadjuvant nivolumab/chemotherapy, rates that still allow room for improvement (https://cancerres.aacrjournals.org/content/81/13_Supplement/CT003).

Despite the excitement over these studies, it remains to be determined whether the degree of pathological response is predictive of disease free and overall survival in NSCLC patients treated with neoadjuvant immunotherapy with or without chemotherapy. It is however notable that the association between pathological response and survival has been clearly shown following neoadjuvant therapy for breast cancer[25]. Regarding NSCLC, longer term results were recently updated from the NADIM trial and demonstrated an OS of 81.9% at 36 months and 78.9% at 42 months in the ITT populations, markedly higher than that of historical controls. Further evidence of the potential survival benefit of immunotherapy in earlier stage patients was also recently demonstrated by the IMpower010 study of adjuvant immunotherapy[11]. In NSCLC patients with completely resected, PD-L1+, stage IB-III disease, investigators reported an improvement in DFS (HR 0.66) in the immunotherapy arm.

1.4.2 Non-ablative doses of radiation will potentiate anti-PD-L1 therapy in PD-L1 +ve and –ve tumors
The immuno-modulatory effects of radiation cited below and the results of preclinical studies combining radiation with immune checkpoint inhibitors strongly suggest that combination radio-immunotherapy may potentiate the anti-tumor effects of PD1 blockade in PD-L1 positive tumors[26-29]. Furthermore, the induction of PD-L1 expression in tumor and immune cells by radiation may render PD-L1 negative tumors more susceptible to anti-PD1 therapy[30]. Given the emerging data on the high pathological response rates from following neoadjuvant ICIs in early NSCLC, we postulate that the addition of non-ablative SBRT to nivolumab and chemotherapy will significantly increase the rate of pathological response compared to nivolumab/chemotherapy alone. This concept was recently born out in a single

center, phase 2 trial from Weill Cornell, which randomized NSCLC patients with clinical stage I-IIIA disease to either neoadjuvant nivolumab (PD-L1 inhibitor) or nivolumab plus non-ablative stereotactic body radiotherapy (8 Gy x 3)[15]. Major pathological response was observed in just two (6.7% [95% CI 0.8–22.1]) of 30 patients in the nivolumab monotherapy group, but in 16 (53.3% [34.3–71.7]) of 30 patients in the nivolumab plus radiotherapy group. The difference in the major pathological response rates between both groups was significant (crude odds ratio 16.0 [95% CI 3.2–79.6]; p<0·0001). In the 16 patients in the dual therapy group with a major pathological response, eight (50%) had a complete pathological response, compared to no patients in the monotherapy group. Although it might be expected that patients receiving SBRT would have a higher pathologic response regardless of immune response (given the local ablative effect), it should be noted that the doses used are non-ablative and that even full-dose SBRT only leads to CPR in 60% of patients in this short treatment window (MISSILE)[31]. Additionally, evidence of an abscopal immune effect induced by the radiation therapy was suggested in this trial by the sterilization of biopsy proven mediastinal lymph node metastases (not included in the SBRT field) in 4 of 6 patients (66%) in the dual therapy arm, compared to just 1 of 7 patients (14%) in the monotherapy arm. The addition of SBRT was well tolerated and did not increase adverse events. This study provides strong evidence to proceed with a trial of non-ablative SBRT with combined chemotherapy/immunotherapy.

1.4.3 Hypothesis

In this randomized trial we will test the hypothesis that non-ablative doses of radiation delivered in combination with nivolumab and chemotherapy will lead to a significant improvement in pathological complete response rates compared to preoperative nivolumab/chemotherapy alone. We will also test the hypothesis that the addition of non-ablative SBRT to neoadjuvant nivolumab and chemotherapy will significantly improve mediastinal nodal downstaging, major pathologic response rates, and disease and event-free survival. The demonstration that safe, non-ablative doses of radiation can be a potent immuno-modulator in this setting will be a paradigm shift and will set the stage for further evaluation of this strategy in NSCLC and other solid tumors.

2.0 BACKGROUND

2.1 Cancer and immune system function

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop multiple strategies to evade immune-mediated killing allowing tumor growth and progression. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 is one such protein that is upregulated in a broad range of cancers with a high frequency. Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling peripheral T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and its expression by tumors is one mechanism of innate or acquired tumor immune resistance. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell[32,33]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination[34].

Based on in vitro studies and extensive clinical data, antibodies that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells[35]. The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung[37], suggesting that an antitumor immune response is beneficial to patients. Based on these findings, anti-PD1 antibodies are used therapeutically to enhance antitumor immune

responses in patients with cancer, lung cancer in particular. Results of several clinical trials in patients with advanced disease have confirmed this hypothesis.

2.2 Nivolumab in Solid Tumors

2.2.1 Preclinical overview

Nivolumab Background

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (JP, Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies.

2.2.2 Summary of clinical experience

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies as described in the USPI and SmPC. Results of clinical studies of nivolumab alone and in combination are summarized in the following additional studies with available data for the indications listed below.

NSCLC

• CA209026: completed Phase 3 study of nivolumab in subjects with Stage IV or recurrent PD-L1+ NSCLC

• CA209012: completed Phase 1 study with nivolumab in combination with ipilimumab, platinum-based chemotherapy or erlotinib in subjects with treatment-naive Stage IIIB/IV NSCLC

• CA209384: completed Phase 3b/4 study of nivolumab monotherapy in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-squamous and squamous)

• ONO-4538-04: completed Phase 1, open-label study of nivolumab in combination with chemotherapy in Japanese subjects with Stage IIIB/IV or recurrent NSCLC

• CA209907: ongoing Phase 2, open-label, single-arm safety study of nivolumab in participants with advanced or metastatic NSCLC who have progressed during or after receiving at least one prior systemic regimen

• ONO-4538-52: ongoing Phase 3 study with nivolumab in combination with carboplatin, paclitaxel, and bevacizumab in subjects with Stage IIIB/IV or recurrent non-squamous NSCLC

2.2.3 Pharmacokinetics and Product Metabolism

Nivolumab PK in patients with cancer was assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab. The PK of nivolumab as monotherapy was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single-dose or as multiple-doses of nivolumab as a 60-minute infusion every 2 or 3 weeks. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg
administered every 2 weeks (Q2W). Based on a population pharmacokinetic (PPK) analysis using data from patients with several tumor types, including melanoma, NSCLC, and RCC and a time varying clearance (CL) model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 26% resulting in a geometric mean steady-state clearance (CLss) (% coefficient of variation [CV%]) of 7.91 mL/h (46%) in subjects with metastatic tumors. The decrease in CLss is not considered to be clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma. The geometric mean [CV%] volume of distribution at steady-state (Vss) is 6.6 L (24.4%), and

elimination half-life (t1/2) is 25 days (55.4%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 4-fold. PK differences across multiple tumor types were explored, and in general there was no clinically meaningful difference, due to a flat dose/exposure-response (E-R) relationship between nivolumab and efficacy/safety. The PK of nivolumab was assessed in the adolescent (≥ 12 to 17 years) and pediatric (< 12 years) subjects. Based on the covariate analysis, adolescent and younger pediatric subjects had nivolumab baseline CL values that were 36% (95% CI: 22-48%) and 62% (52-71%) lower than in adult 1L melanoma subjects, respectively. In addition, the adolescent and pediatric subjects had 16% (8.3-22%) and 32% (25-39%) lower nivolumab VC, respectively, than adult subjects. Refer to Section 5.2.1.2 for detailed information on nivolumab exposures in pediatric and adolescent subjects. The PK of nivolumab were assessed using a PPK approach when nivolumab and ipilimumab were administered in combination. When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was unchanged. These are unlikely to be clinically relevant given the flat dose-response observed between nivolumab and efficacy and safety. Nivolumab E-R relationships for efficacy and safety were evaluated for nivolumab monotherapy and in combination with ipilimumab. The dose range of 1 mg/kg every Q2W to 10 mg/kg Q2W was evaluated for nivolumab monotherapy in melaoma, RCC, and NSCLC. Generally, a flat E-R relationship was observed over this dose range between nivolumab and clinical endpoints such as the hazard of death, probability of objective response (OR), adverse events (AEs) leading to discontinuation or death (AE-DC/D), and/or Grade 3+ AEs, and a 3 mg/kg Q2W dose regimen was approved for these and additional indications. For NSCLC, there was a trend of additional benefit (especially in objective response rate [ORR]) at 3 mg/kg Q2W, when compared to 1 mg/kg Q2W, which had a small sample size. Therefore, a flat E-R relationship could only be confirmed from 3 mg/kg Q2W to 10 mg/kg Q2W for NSCLC. Further E-R analyses demonstrated that the benefit-risk profiles of nivolumab 240 mg Q2W and 480 mg every 4 weeks (Q4W) are comparable to 3 mg/kg Q2W; flat dose nivolumab monotherapy regimens were subsequently approved in some regions for existing and additional indications including melanoma, RCC, NSCLC, SCLC, SCCHN, CRC, UC, cHL, HCC, and esophageal squamous cell carcinoma (ESCC). Flat dose regimen 360 mg every 3 weeks (Q3W) nivolumab was similarly evaluated and approved recently as combination therapy with ipilimumab and platinum-doublet chemotherapy in NSCLC.

2.2.4 Safety

Overall risks

The monitoring of subject safety during and after a clinical study with nivolumab, including any special monitoring precautions, tests, or observations, and the proper means of recording and reporting adverse safety information (ie, AEs and abnormal laboratory values) will follow the procedures outlined in the specific study protocol. Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized below and described in detail in Appendix B. The overall safety experience with nivolumab is based on experience in approximately 26,405 subjects as either monotherapy or in combination with other therapeutics. In general, for monotherapy, the safety profile is similar across tumor types. The exception is pulmonary inflammation AEs and hepatic AEs, which may be numerically greater in subjects with NSCLC and HCC, respectively, possibly because in some cases, it may be difficult to distinguish between nivolumab-related and unrelated causes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created (see Section 5.5). Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and

renal AEs. The frequency of select AE categories is provided in the sub-sections for individual indications under Section 5.5. It is also useful to consider the management of nivolumab-related AEs by organ category as the diagnostic work-up often requires excluding other potential diagnoses and, when appropriate, instituting specific management principles as outlined in the subsequent subsections and Appendix 4. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. As referenced in Section 5.4, in select tumors combinations containing nivolumab + ipilimumab, nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy, nivolumab + cabozantinib, and nivolumab + fluoropyrimidine + platinum-containing chemotherapy have been approved in the US and/or EU. The combination of nivolumab+ipilimumab results in a safety profile with similar types of AEs compared to each agent alone, but in some cases, with a greater frequency. The optimal doses for nivolumab + ipilimumab combination continue to be evaluated and may vary by tumor type. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms. As described in Section 5.8, it is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as *P. jiroveci* (formerly *P carinii*) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

Nivolumab

Adverse Event Profile of nivolumab plus chemotherapy

2.2.5 Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCCHN, malignant pleural mesothelioma (MPM), UC, gastric cancer (GC), gastroesophageal junction cancer (GEJC), esophageal cancer (EC), HCC, CRC. In confirmatory trials, nivolumab demonstrated significant clinical benefit as monotherapy, and in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies.

Clinical data

The use of monoclonal antibodies that target immune checkpoints has revolutionized lung cancer treatment. Among other therapeutic antibodies, several NSCLC trials have demonstrated the efficacy of nivolumab in patients with advanced NSCLC. A trial of nivolumab in 129 heavily pretreated patients with NSCLC was originally reported[38]. The objective response rate was 17% and was similar in squamous and non-squamous NSCLC. Impressively the duration of response was 17 months; an

unprecedented duration of response compared to that seen after either chemotherapy or even early oncogene targeted therapy. These impressive response rates translated into a significant improvement in survival (1 year: 42% and 2 year: 24%). Rizvi *et al* subsequently reported the results of a phase II trial of nivolumab monotherapy in 117 patients with refractory advanced squamous cell lung cancer[39]. The objective response rate was 14.5% and an additional 26% of patients had stable disease.
Based on these findings, nivolumab has been approved for use in the second line setting for NSCLC patients in the US, EU, and additional regions. For first line treatment, nivolumab and ipilimumab combination therapy demonstrated clinical benefit in subjects with metastatic NSCLC with ≥ 1% PD-L1+ tumor expression and has therefore been approved for use in this population in the US. Additionally, nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy demonstrated clinical benefit as first-line treatment in subjects with metastatic NSCLC and has been approved for use in this population[40]. In CA209026, an open-label, randomized, Phase 3 study of nivolumab vs investigator's choice chemotherapy (ICC) as first-line therapy for Stage IV or recurrent PD-L1+ NSCLC, nivolumab monotherapy did not demonstrate superior progression free survival (PFS) per Independent Radiologic Review Committee (IRRC) compared to the ICC (platinum-doublet chemotherapy) in patients with ≥ 5% PD-L1+ tumor expression. PFS per IRRC in the all randomized population was similar to the population with ≥ 5% PD-L1+ tumor expression. However, nivolumab monotherapy appears to have clinical activity as first-line treatment in these populations, as evidenced by similar OS with the ICC group, despite the fact that 60% of subjects in the ICC group received subsequent nivolumab. The ORR of 26% in the nivolumab group, although numerically lower than the ORR of 33.5% in the ICC group, is associated with a longer duration of response and also represents evidence of clinical activity for nivolumab monotherapy in this setting.

2.2.6 Nivolumab and neoadjuvant targeting of the PD1/PD-L1 pathway in NSCLC
Because of its favorable toxicity profile and these encouraging early results using nivolumab in advanced NSCLC, clinical trials have recently been undertaken in early stage NSCLC. Forde et al. published the first neoadjuvant trial with nivolumab alone in NSCLC, utilizing two cycles of neoadjuvant therapy[12]. This trial reported an MPR of 45% and a CPR rate of 15%. Rates of MPR and CPR with nivolumab alone were subsequently found to be lower in the ITT monotherapy arm of the NEOSTAR trial (17% and 9% respectively), but were found to improve with the addition of ipilumimab to 33% and 29%, demonstrating strong rationale for combination therapy to modulate the immune reponse[13]. Unfortunately, this particular combination was less well tolerated and fewer patients in the combination arm completed therapy. The NADIM trial, which utilized three cycles of neoadjuvant nivolumab/chemotherapy in stage IIIA NSCLC patients, demonstrated a remarkable CPR rate of 63% (with downstaging in 90% of patients) and has generated tremendous excitement for nivolumab combination therapy with chemotherapy in the neoadjuvant setting[13]. This strategy was tested in the phase 3 CheckMate-816 trial, the results of which have been recently presented (AACR 2021, ASCO 2021). This trial randomized patients with stage IB-IIIA NSCLC to three cycles of neoadjuvant chemotherapy or three cycles of neoadjuvant chemotherapy with nivolumab (360 mg Q3W). The primary endpoint was CPR. Approximately 80% of patients went on to definitive surgery after neoadjuvant therapy, among whom the CPR rate was markedly improved to 30.5% with nivolumab/chemotherapy compared to just 3.2% with chemotherapy alone. Improvements in CPR were seen in the stage IB-II patients in addition to the stage III patients and were fairly uniform across subgroups. This correlated with improvements in MPR in the groups as well, 36.9% in the nivolumab/chemotherapy arm versus 8.9% in the chemotherapy alone arm in the entire ITT population. Depth of pathologic response was significantly greater with nivolumab/chemotherapy, with a median of only 10% viable tumor cells in that arm compared to 74% in the chemotherapy only arm. In addition to the difference in pathologic response rates, investigators recently reported surgical safety data of CheckMate-816 (https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.8503). Remarkably, almost all surgical outcomes favored the nivolumab/chemotherapy arm over the chemotherapy alone arm. Although not all statistically significant, in the nivolumab arm more patients made it to surgery (83% vs. 75%), surgery

took less time (184 vs. 217 minutes), more resections were performed minimally invasively (30% vs. 22%), less pneumonectomies were required (17% vs. 25%), and less surgery-related grade 3-4 AEs were reported (11% vs. 15%). The safety and surgical outcome data thus reported to date from CheckMate-816, along with the notable improvement in CPR, strongly support this neoadjuvant option for patients with resectable NSCLC.

2.2.7 Radiation and tumor immunity

Radiation therapy is an essential component of the treatment of many solid tumors. Delivered alone, or in combination with chemotherapy, the aim of radiotherapy is to provide definitive and potentially curative tumor eradication for localized disease or palliation in the metastatic setting. In such instances the benefits of radiotherapy are generally attributed to a direct cytoreductive or cytocidal effect mediated by radiation induced DNA damage. However, emerging pre-clinical evidence suggests that radiotherapy, in addition to its direct cytocidal effects, can be a potent modulator of the local intra-tumoral and possibly systemic anti-tumor immune response, and thereby have specific anti-tumor effects beyond its direct effects on the cancer cells. Ionizing radiation may potentiate antitumor immunity by acting directly on tumor cells rendering them more immunogenic and by inducing adjuvant signals in the tumor microenvironment in a manner that favors an anti-tumor immune milieu. For example, radiation by acting directly on tumor cells can lead to "immunogenic cell death"; a phenomenon characterized not only by simple neo-antigen release from cancer cells but also by the release of various danger signals that favor dendritic cell maturation and activation, and the recruitment of tumor antigen specific CD8 T-cells[41-42]. These signals include the release of the nuclear protein high mobility group box 1, adenosine tri-phosphate as well as the translocation of calreticulin from the endoplasmic reticulum to the plasma membrane where it acts as an "eat me" signal for antigen presenting cells[43-45]. These cell death-associated molecules bind their respective receptors on intra-tumoral immature dendritic cells leading to activation of the inflammasome with DC maturation, secretion of IL1ß and evolution of antigen specific CD8 T cells[46]. Radiation can enhance tumor antigen presentation by up-regulation in cancer cells of MHC class I molecules that are necessary for endogenous peptide presentation as well as by up-regulating the expression of tumor specific antigens such as cancer testis antigens[47,48]. Radiation can also render tumor cells more susceptible to T cell cytolytic activity by enhancing Fas gene expression [49]. Beyond its direct effect on cancer cells, ionizing radiation can modify the tumor microenvironment by triggering a cytokine/chemokine mediated inflammatory response with the recruitment of immune/inflammatory cells including monocytes, macrophages, DCs as well as effector T cells. Other radiation induced changes in the tumor microenvironment demonstrated in preclinical experiments include the up-regulation in endothelial cells of the adhesion molecules VCAM-1 and ICAM-1 that facilitate trafficking of immune cells into the tumor microenvironment [50].

Many of these radiation-induced effects on the cancer cell and its microenvironment have been demonstrated to occur in human cancer cell lines and preclinical models even with sub-lethal doses of radiation [51]. Despite its role in generating or potentiating an anti-tumor immune response, ionizing radiation can also contribute to an immuno-suppressive tumor microenvironment by the recruitment of myeloid derived suppressor cells, tumor associated macrophages and T-regs as well as by the inducing the secretion of the immunosuppressive cytokine, TGFß [52-54]. The net balance between the pro and anti-immunogenic effects of radiation therapy likely influences whether or not radiation results in an effective anti-tumor immune response. However, the currently available evidence supports the concept that radiation even at sub lethal doses can render cancer cells more immunogenic.

2.2.8 Radiation combined with immune checkpoint inhibition

Despite the success of radiation in controlling local disease, the majority of patients develop either regional or systemic relapse. Clearly the pro-immunogenic effects of radiation are insufficient to either initiate or sustain an effective and durable anti-tumor immune response. Combining radiotherapy with immune checkpoint blockade has been tested in several preclinical models. In an orthotopic mouse model of glioma, stereotactic radiation (10Gyx1) was given in combination with an anti-PD1 antibody[26]. Long-

term cures were observed in some mice treated by combination therapy but in none treated by either modality alone. Post-mortem examination showed that the brains of cured animals contained increased cytotoxic T cells. Furthermore, when cured mice were re-challenged several months later by flank injections of isogenic tumor cells, they failed to establish flank tumors in contrast to tumor naïve mice consistent with a systemic tumor antigen-specific memory immune response. Using a breast cancer mouse model with a primary tumor on one flank and a secondary tumor on the other flank, Dewan et al tested various fractionation schemes of radiation (20Gyx1, 8 Gyx3 and 6Gyx5) given with or without an anti-CTLA-4 antibody [27]. Radiation was delivered to the primary but not to the secondary site. Treatment with the antibody alone had no discernible effect on tumor growth. All fractionation schemes of radiation resulted in tumor growth delay in the irradiated primary tumor. Combination therapy resulted in enhanced tumor response at the primary site in all radiation treated animals. A tumor response at the secondary non-irradiated site (an abscopal effect) occurred only in mice treated with fractionated radiotherapy and was abrogated by T cell depletion [27]. Dovedi et al reported that in animal models of triple negative breast cancer, melanoma and colon cancer treatment with 5 daily fractions of radiation (2Gyx5) and anti-PDL1 antibody was curative in 66% of mice [29]. Long-term survival was associated with efficacious CD8+ T–cell responses and the induction of tumor antigen-specific memory immune response protecting against isogenic tumor re-challenge. The authors also found that treatment sequencing was critical for a favorable outcome with long-term survival associated with concurrent rather than sequential administration of combined therapy. The dose and fractionation of radiation necessary for optimal immune potentiation as well the exact sequencing of immune checkpoint inhibition have yet to be fully investigated. However, the preclinical studies by Dewan and Dovedi highlight the importance of using multiple fractions of radiation and concurrent administration of immune checkpoint blockade for generating efficacious CD8 T-cell responses necessary for tumor control and generation of antigen-specific immune memory to protect against re-challenge. This synergism between radiation and immune checkpoint inhibition is currently being tested in controlled clinical trials in some advanced solid tumors. Interestingly there are at least three well documented case reports of an abscopal effect observed in two patients with metastatic melanoma and two patients with metastatic lung cancer all of whom were treated by targeted hypofractionated radiation and ipilumumab [55-57]. Both patients with NSCLC had refractory disease and required localized multiple fractions of radiation to a metastatic site along with anti-CTLA-4. A complete clinical response was documented in both patients including in metastatic sites outside the radiation field. In the two patients with melanoma, tumor regression was associated with evidence of epitope spreading, strongly suggesting an immune contribution to the clinical outcome.

Perhaps the most compelling evidence of the additive effects of radiation to immune response come from the recently completed clinical trial described above from Altorki et al., which randomized NSCLC patients with clinical stage I-IIIA disease to either neoadjuvant nivolumab (PD-L1 inhibitor) or nivolumab plus non-ablative stereotactic body radiotherapy (8 Gy x 3)[15]. Major pathological response was observed in just two (6.7% [95% CI 0.8–22.1]) of 30 patients in the nivolumab monotherapy group, but in 16 (53.3% [34.3–71.7]) of 30 patients in the nivolumab plus radiotherapy group. Using deconvolution of RNA sequencing data to compare the immune phenotypes between pre- and post-treatment samples, investigators found no differences in patients treated with durvalumab monotherapy. However, in patients treated with SBRT and durvalumab, post-treatment samples showed significant differences compared to pre-treatment samples with increases in mature and immature dendritic cells, M1 and M2 macrophages, fibroblasts, and MHC-I gene expression in the post-treatment samples. In particular, in patients with MPR, the xCell deconvolution-derived immune score increased significantly. This data, along with the abscopal effects noted in non-radiated lymph nodes, provides strong clinical evidence of an immune priming effect of low dose radiation therapy.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Patient has histologically or cytologically proven clinical stages IIA (tumors > 4 cm), IIB, IIIA, or IIIB (T3 or T4, N2) NSCLC (AJCC version 8) and is considered eligible for surgical resection with curative intent. Patients with 2 primary non-small cell lung cancers are allowed.
2. Measurable disease, as defined by RECIST v1.1.
3. Parenchymal lung tumor deemed to be amenable to treatment with sub-ablative stereotactic body radiation therapy, as determined by a co-investigator from Radiation Oncology
4. Written informed consent and HIPAA obtained from the subject prior to performing any protocol-related procedures.
5. Age > 18 years at time of study entry
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Adequate normal organ and marrow function as defined below:
    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L (> 1500 per mm3)
    - Platelet count ≥ 100 x 109/L (>100,000 per mm3)
    - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
    - AST (SGOT)/ALT (SGPT), and alkaline phosphatase ≤ 2.5 x institutional upper limit of normal (ULN).
    - Serum creatinine CL>50 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:
Creatinine CL (mL/min)
= Weight (kg) x (140 – Age) . 72 x serum creatinine (mg/dL)
Females:
Creatinine CL (mL/min)
= Weight (kg) x (140 – Age) x 0.85 72 x serum creatinine (mg/dL)

8. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

9. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
10. No prior therapy for their lung cancer.

3.2 Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Participation in another clinical study with an investigational product during the last 3 weeks.
2. Active other primary malignancy excepting:

- Malignancy treated with curative intent and with no known active disease and of low potential risk for recurrence.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ, in-situ urinary bladder cancer, treated localized prostate cancer and ductal carcinoma-in situ.

3. Current or prior use of immunosuppressive medication within 14 days before the first dose of nivolumab, with the exceptions of intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection), corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid, and steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
4. Patients with Grade ≥2 neuropathy
5. Previous receipt of immunotherapy (such as anti-PD1, anti-PDL1 or anti-CTLA4 monoclonal antibody therapy)
6. Active or prior documented autoimmune or inflammatory disorders that has required systemic treatment in the past year (including inflammatory bowel disease [e.g., colitis or Crohn's disease systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). No active diverticulitis within the previous 3 months. The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
7. History of allogeneic organ transplant.
8. History of hypersensitivity to nivolumab or any excipient.
9. Uncontrolled intercurrent illness that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
10. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), active hepatitis B (known positive HBV surface antigen (HBsAg) result), active hepatitis C.
11. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of nivolumab monotherapy.
12. History of interstitial lung disease, idiopathic pulmonary fibrosis, pneumonitis (including drug induced), or evidence of active pneumonitis on screening chest CT scan.
13. Receipt of the last dose of therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, or other investigational agent) for an accepted other malignancy as defined in Section 3.3.2 within 30 days prior to the first dose of study drug for lung cancer.

4.0 REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 Registration

Eligible subjects will be identified by the Principal Investigator's and co-investigators from the Thoracic or Medical Oncology clinics at Montefiore Medical Center / Albert Einstein College of Medicine or collaborating institutions. Individuals will be approached and informed of the rationale for the study, investigational nature of the protocol and study drug and the voluntary nature of participation, potential

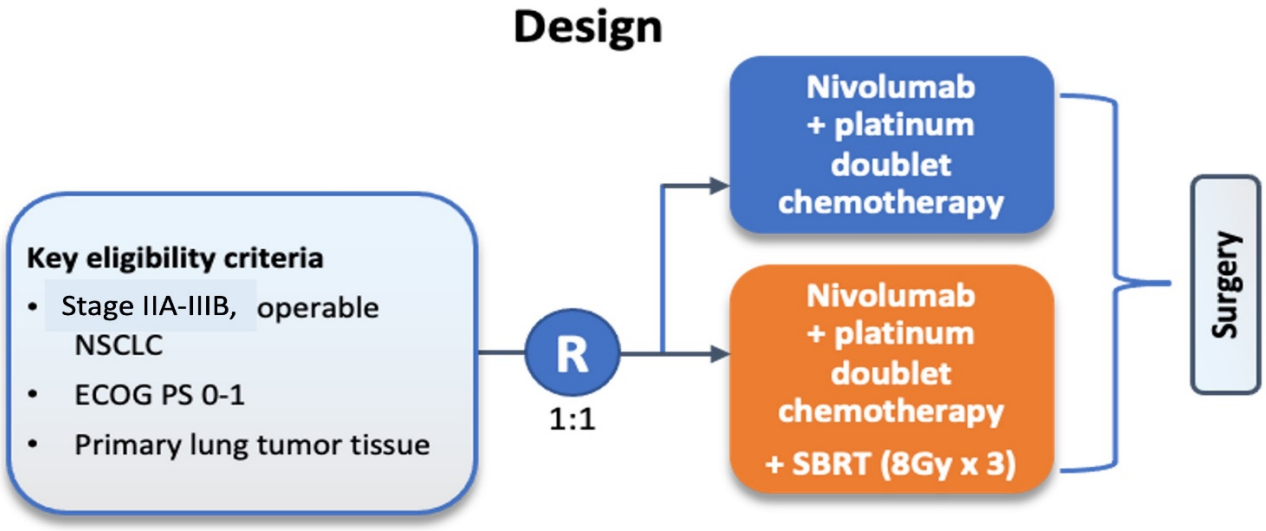
risks and benefits, alternatives to participation, and study procedures. Individuals will have the opportunity to read the written informed consent document with the understanding that should they decide not to participate, they will still be able to receive any available therapy off-trial. Potential subjects will also have the opportunity to obtain the advice of their treating physician. Investigators or delegates under their direct supervision will verify the subject's understanding of the investigational and voluntary nature of the study, the potential risks and benefits, study procedures, and alternatives prior to signing of the written informed consent. Those who wish to participate in the trial will be required to sign an informed consent form after all their questions are answered. Subjects will be registered to the trial once they have met the eligibility criteria. Documentation of the consent process and that written consent was conducted must be documented in the subject's medical record.

4.2 Randomization

At the time of study registration, subjects will be stratified by (PD-L1 TPS <1% versus ≥1% and by pretreatment node positivity (yes/no) and then will be randomized 1:1 between the two study arms with the aid of the study statistician, using a modified permuted block treatment allocation scheme.

5.0 STUDY DESIGN

This is a randomized open label phase II trial utilizing preoperative anti-PD1 antibody nivolumab and chemotherapy, with or without concurrent non-ablative stereotactic radiation, followed by surgical resection.



5.1 Treatment Plan

Patients with biopsy proven NSCLC clinical stages IIA (tumors ≥ 4 cm), IIB, IIIA, and IIIB will be randomly assigned to receive 3 preoperative cycles of nivolumab and chemotherapy, followed by surgical resection, with or without non-ablative stereotactic radiotherapy given during the first cycle of nivolumab/chemotherapy. Patients randomized to the nivolumab/chemotherapy alone arm will receive three cycles of nivolumab at a dose of 360 mg every three weeks along with a standard-of-care platinum-based chemotherapy doublet (such as cisplatin or carboplatin plus pemetrexed or carboplatin plus paclitaxel for non-squamous histology, cisplatin or carboplatin plus docetaxel, paclitaxel, or gemcitabine for squamous NSCLC). Patients in the radio-immunotherapy arm will also be treated with three cycles of nivolumab/chemotherapy plus radiotherapy delivered in 3 daily fractions of 8 Gy starting after the first cycle of nivolumab and just prior to the second. This delivered non-ablative radiation dose of 24 Gy is equivalent to a biologically effective dose (BED) of 43.2 Gy, which is significantly lower than the standard therapeutic dose for ablation of T1-T2 NSCLC (BED>100Gy). The objective is to induce

immunogenic cell death, enhance antigen presentation, and increase cytotoxic T lymphocyte activity without tumor ablation. This non-ablative dose of radiation is selected based on the results of studies preclinical studies showing that the 8 Gy x 3 regimen resulted in significant immune modulation in preclinical models as well as a recently published clinical trial using the same regimen with neoadjuvant nivolumab[13]. A research core biopsy for the collection of tumor tissue is suggested but not mandatory. If a tissue biopsy has already been obtained for diagnostic purposes, a core biopsy may be performed for research purposes only to obtain tumor tissue. If a tissue biopsy has not been performed yet for diagnostic purposes, a core biopsy may be performed for diagnosis and tissue will be obtained for research purposes. Tissue from the preoperative core samples and from the resected surgical specimens will be stored for future correlative studies (multiplex immunofluorescence, whole tumor RNAseq, etc). Although PDL-1 expression is not required for eligibility, preoperative and post-operative tissue will be assessed for PDL-1 expression. RepeatCT will be performed 2-4 weeks after completion of neoadjuvant therapy. All patients will proceed to surgical resection 4-8 weeks after completing the third cycle of nivolumab/chemotherapy, regardless of local response assessment and provided that repeat imaging shows no evidence of systemic disease. If the participant receives fewer than 3 cycles of neoadjuvant immunotherapy, he/she can remain in the study and should undergo surgery within 4-8 weeks following the last dose of the protocol therapy. Delays caused due to federal/state holidays, scheduling conflicts, or any other unforeseen circumstance may result in postponement of the next applicable treatment course of the subject.

5.2 Chemotherapy

The study treatment(s) to be used in this trial are outlined below:
All participants will receive standard-of-care platinum-based doublet chemotherapy (PDC) regimens (NCCN NSCLC guideline version 1.2023) along with nivolumab for 3 cycles every 3 weeks. Either Cisplatin or Carboplatinum can be utilized as the platinum agent. If Cisplatin is opted for, Carboplatinum (AUC=5-6) can be used instead of Cisplatin (75mg/m2) from cycle 2 for Cisplatin induced neuro/oto/nephrotoxicity as long as patient remains eligible for doublet chemotherapy.

Participants with nonsquamous tumors will receive pemetrexed (500 mg/m2) or paclitaxel (175-200mg/m2). Participants with squamous tumors will receive either paclitaxel (175-200 mg/m2) or docetaxel (75 mg/m2 on day 1) or gemcitabine (1000 mg/m2 on days 1, 8) as part of the platinum-based doublet. Cycles will be every 3 weeks and a maximum of a 2-week delay will be permitted for resolution of toxicities.

5.2.1 Dose Modification

Chemotherapy dose modifications will be based on standard of care. Below are listed general dose modification guidelines. If appropriate, the investigator may attribute each toxicity event to cisplatin, pemetrexed, gemcitabine, paclitaxel, docetaxel or nivolumab (either to the agent alone or to the combination of these agents). Dose modifications must be based on the maximum toxicity experienced during a cycle. Treatment related toxicity must resolve to Grade ≤1 or baseline before resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade >2. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any particular component will have

that agent discontinued. Nivolumab dose reductions are not permitted. Nivolumab treatment may be interrupted or discontinued due to toxicity. Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to that chemotherapy agent. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications in the approved product labels. Please refer to approved local product labels for dose modifications regarding the chemotherapy regimen for cisplatin or carboplatin/pemetrexed, cisplatin or carboplatin/paclitaxel, cisplatin/gemcitabine and cisplatin/docetaxel.

The following dose levels and dose modification are recommended if a dose modification is needed. If the toxicity is related to the chemotherapy agents dose should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications. If the toxicity is related to Nivolumab, it should be discontinued. Participants may have chemotherapy discontinued and continue on nivolumab alone. Similarly, participants may discontinue nivolumab and continue on chemotherapy alone during the 3 cycles of therapy if appropriate. See section 5.2.3 for additional information.

Please note that if one or more of the chemotherapy agents are interrupted, all 3 therapies (cisplatin/carboplatin, paclitaxel/gemcitabine/pemetrexed/docetaxel, and nivolumab) should be withheld for the duration of the interruption. If only nivolumab is interrupted, chemotherapy may continue during the nivolumab interruption. However, if the complication leading to the nivolumab interruption would be made worse by continued chemotherapy (i.e. hepatitis), the chemotherapy should either be interrupted or reduced.

5.2.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)
Dose Modification and Toxicity Management for Immune-related AEs Associated with Nivolumab
AEs associated with nivolumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of nivolumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of nivolumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue nivolumab and administer corticosteroids.

5.2.3 Chemotherapy Dose Modifications
Please refer to approved local product labels for dose modifications regarding the chemotherapy regimens used. The following dose levels and dose modification are recommended if a dose modification is needed. Please note that dependent on starting dose opted for, two dose modification guidelines are listed for Carboplatinum and paclitaxel:

Dose levels:
Cisplatin dose level 0 75mg/m2, dose level -1 56mg/m2, dose level -2 38mg/m2

Carboplatinum
Starting dose AUC 6: dose level 0, dose level -1 AUC 4.5, dose level -2 AUC 3
Starting dose AUC 5: dose level 0 AUC 5, dose level -1 AUC 3.75, dose level -2 AUC 2.5

Paclitaxel
Starting dose 200mg/m2: dose level 0 200mg/m2 dose level -1 150mg/m2, dose level -2 100mg/m2

Starting dose 175mg/m2: dose level 0, dose level -1 131mg/m2, dose level -2 88mg/m2

Pemetrexed dose level 0 500 mg/m2, dose level -1 375 mg/m2, dose level -2 250 mg/m2

Docetaxel dose level 0 75 mg/m2 dose level -1 56 mg/m2, dose level -2 38 mg/m2

Gemcitabine dose level 0 1000 mg/m2, dose level -1 750 mg/m2, dose level -2 500 mg/m2

Gemcitabine dose needs to be held on day 8 of chemotherapy cycle for ANC<1000, platelet count <75K. If a gemcitabine dose is held, subsequent cycles need to be given with a dose reduction.

Non-ablative SBRT (Arm 2 only)

Note: "SBRT" in this protocol refers to localized and conformal radiotherapy delivered over a course of three fractions and utilizing a dose of 8 Gy per fraction. This may be achieved using 3D conformal techniques or intensity modulated radiotherapy (IMRT), as long as the radiotherapy guidelines in Sections 5.3.1 to 5.3.5 are followed.

5.3.1 SBRT Timing

SBRT will be delivered near the conclusion of cycle 1. The intent is to deliver SBRT on three consecutive days when the concentration of radiosensitizing chemotherapy agents in the subject's system is at a minimum, to minimize toxicity risks. It is expected that some subjects may not receive SBRT on three consecutive days due to machine breakdown, inclement weather, or other logistic issues. Subjects must not receive SBRT within 72 hours after a cisplatin or carboplatin infusion.

5.3.2 Immobilization, Simulation, and Localization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e.,< 5%). Special considerations will be made to account for the effect of internal organ motion (e.g., breathing) on target positioning and reproducibility. Acceptable maneuvers include reliable abdominal compression, accelerator beam gating with the respiratory cycle, active breath-holding techniques, and use of 4D simulation CT to generate internal target volumes (ITVs). Internal organ inhibition maneuvers must be reliable enough to ensure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., <5%). Computed tomography will be the primary image platform for targeting and treatment planning. Axial acquisitions with gantry 0 degrees and spacing ≤ 3.0 mm between scans in the region of the tumor are required. Images will be transferred to thetreatment planning system for radiotherapy planning. Verification CT scans should be obtained immediately before each treatment toensure proper alignment of the geometric center (isocenter) of the simulated fields. Verification CT scans and/or portal films during or following each treatment may beacquired at the discretion of the treating physician.

5.3.3 Target Volumes

Gross tumor volume (GTV) for the primary lung tumor will be drawn on simulation CT imaging, using appropriate window levels. Other imaging modalities (e.g., PET, MRI) may be fused to simulation CT scans to aid with localization of target lesions. Respiratory motion management is required. A deep inspiration breath hold (DIBH) technique may be utilized to eliminate respiratory motion. In other cases, 4D CT simulation will be employed. If 4D CT simulation is used, GTVs should be generated on each CT phase

that will be used for treatment (typically 4/10 phases if respiratory gating is employed or 10/10 phases if thepatient will be treated while breathing freely). These GTVs will be combined to form internal target volumes (ITVs).No clinical target volumes (CTVs) will be employed in this protocol.
GTVs or ITVs will be expanded to form planning target volumes (PTVs), usingexpansions of 4-5 mm in all directions. Expansion may be increased by up to 5 additional mm in the craniocaudal directions if there is concern for unmeasured respiratory motion (e.g., in cases of limited 4D CT quality).

5.3.4 SBRT Dosing and Target Coverage
The SBRT dose for all study subjects will be 8 Gy x 3. At least 95% of the PTV should receive the full prescription dose. If this cannot be achieved while respecting normal tissue constraints, the portion of the PTV abutting/overlapping a radiosensitive structure may be excluded from the target coverage evaluation structure ("PTV_eval").

5.3.5 Critical Structures
Normal tissue structures visualized on the simulation CT will be delineated usingcontouring guidelines established by RTOG: https://www.rtog.org/CoreLab/ContouringAtlases.aspx. The following normal tissue constraints, adopted from NCCN guidelines and RTOG 0813, will be utilized:

	3 Fractions
Brachial plexus	max dose < 24 Gy
Esophagus	max dose < 30 Gy
Great vessels	max dose < 39 Gy
Heart/pericardium	max dose < 30 Gy
Lungs	At least 1500 cc receiving < 12.5 Gy
Skin	max dose < 24 Gy
Spinal cord	max dose < 18 Gy
Stomach	max dose < 27 Gy
Trachea and proximal bronchi	max dose < 30 Gy

5.4. Duration of follow-up
Post-operatively, patients will be followed monthly from the date of the last infusion dose until month 4, at month 6, and subsequently every 6 months for 2 years. Thereafter, patients will be followed yearly until year 5. Patients removed from the study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.
Follow-up imaging will be performed by non-contrast chest CT scan every 6 months for 2 years then yearly thereafter until year 5. Recurrent disease should be pathologically confirmed whenever possible.

5.5 Withdrawal of Subjects from Study Treatment and/or Study
5.5.1 Permanent discontinuation of nivolumab
An individual subject will not receive any further investigational product if any of the following occur in the subject in question:
1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the study supporter, contraindicates further dosing
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
4. Pregnancy or intent to become pregnant

5. Any AE that meets criteria for discontinuation as defined in Section 6.0
6. Adverse event related to nivolumab that is Grade ≥ 3, with the exception of toxicities that do not meet criteria for discontinuation as defined in Section 6.0
7. Grade ≥ 3 infusion reaction
8. Subject noncompliance that, in the opinion of the investigator or study supporter, warrants withdrawal; eg, refusal to adhere to scheduled visits

Initiation of alternative anticancer therapy including another investigational agent

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who are permanently discontinued from receiving investigational product will be followed for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival.

5.5.2 Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

• all further participation in the study including any further follow up (e.g., survival contact telephone calls)
• withdrawal of consent to the use of their study generated data
• withdrawal to the use of any samples

5.6 STUDY PROCEDURES

The Schedules of Assessments during the screening and treatment period is provided below.

Table 1. Schedule of study assessments: Screening and Treatment Period
Visit

Visit (Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)	Screening	Baseline, Cycle 1 (+/- 3 days)	Cycle 2 (+/- 3 days)	Cycle 3 (+/- 3 days)	Pre-operative	Surgical resection	Postoperatively at 2 weeks
Day	-28 to -1	1	22	43	57-71	71-99	106-118
Week	-4 to -1	0	3	6	8-10	10-14	15-17
Nivolumab + chemotherapy		x	x	x			
Arm 2 only: SBRT		x					
Tumor tissue[a]	X					X	
Pregnancy test[b]	X				X		
Physical examination[c]	X	X	X	X	X	X	X
Vital signs (pre- during and post-infusion vital signs assessment[d]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Electrocardiogram[e]	X						
Adverse event / serious adverse event assessment	X	X	X	X	X	X	X

Concomitant medications	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X
Serum chemistry[f]	X	X	X	X	X	X	
Gamma glutamyltransferase	X						
Thyroid function tests[g]	X	X	X	X	X		
Hematology[f]	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	
Coagulation parameters[h]	X				X	X	
Tumor assessment (CT/PET scan)[i]	X						
Tumor assessment (Chest CT scan non-contrast)					X		
ctDNA		X		X			X
Chest X-ray							X

(Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.)

- **a.** Tissue from core biopsies and resected specimens will be stored for future correlative studies and will be requested by lead organization at the end of the trial. A research core biopsy for collection of tumor tissue is suggested but not mandatory.
- **b.** Pre-menopausal female subjects of childbearing potential only.
- **c.** Full physical examination at baseline; targeted physical examination at other timepoints.
- **d.** Vital signs are temperature, blood pressure, pulse rate, and respiratory rate. Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times:
    - At the beginning of the infusion (at 0 minutes)
    - At the end of the infusion (±5 minutes)
    - In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

- **e.** Single screeningECG, and as clinically indicated with abnormal ECG in triplicate.
- **f.** If screening laboratory assessments are performed within 7 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase (GGT) tested at Screening and as clinically indicated.
- **g.** Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
- **h.** Coagulation tests: prothrombin time, APTT and INR – performed at Screening, pre-operative, surgical resection and as clinically indicated.
- **i.** Post-operative CT scans are performed every 6 months for 2 years then yearly until year 5.
- **j.** Subjects in Arm 1 and Arm 2 will receive adjuvant treatment per local guidelines
- **k.** SBRT will be delivered near the conclusion of cycle 1 (see section 5.3.1 for details).
- **l.** Surgical resection will take place 4 -8 weeks after the last dose of nivolumab. Tumor, adjacent normal lung, and lymph node specimens will be obtained from the surgical resection specimen, snap frozen.

m. Standard of care CT/PET scans performed prior to obtaining informed consent and within 60 days prior to C1D1 may be used for screening.

Screening laboratory procedures performed within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

A 12-lead ECG will be recorded for all subjects on study days noted in Section 5.5, Schedule of Study Assessments. ECGs are required during Screening, at Baseline prior to starting study treatment on Cycle 1 Day 1 (C1D1), and at any other time point when clinically indicated. ECGs recorded during the screening period will be single tracing and ECGs recorded at Baseline prior to C1D1 will be obtained in triplicate (with 2-5 minute lag time between each). All 12-lead ECGs should be recorded while the subject is in the supine position. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. At Screening, a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On nivolumab treatment days, vital signs will be measured within an hour prior to start of nivolumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

Table 2. Schedule of study procedures: follow-up for subjects who have completed or discontinued nivolumab treatment

Evaluation	Time since last dose of nivolumab					
	Day (+/- 3)	Months (+/- 1 week)				Every 6 months for 2 years then yearly until year 5 (+/- 2 weeks)
	30	2	3	4	6	
Physical examination	X					X
Vital signs	X					
Weight	X					
Urine hCG or serum BhCG	X					
Concomitant medications	X	X	X			
ECOG performance status	X	X	X		X	X
Adjuvant anti-cancer therapy, if required, as standard of care	X	X	X	X	X	X
Hematology	X	X	X			
Serum chemistry	X	X	X			
Thyroid function tests	X					
Chest X-ray			X			
Tumor assessment (non-contrast chest CT scan)	Every 6 months for 2 years then yearly until year 5					

Tumor assessment (non-contrast Chest CT scan)

Tumor assessments should be performed every 6 months for 2 years then yearly until year 5.

a. Full physical exam
b. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

The following clinical laboratory tests will be performed (see Schedule of study assessments and Schedule of procedures: follow-up) for the timepoints of each test):

- Coagulation parameters: Activated partial thromboplastin time and International normalised ratio to be assessed at baseline and as clinically indicated

- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin
    - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
    - free T3 and free T4 only if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system
- Other laboratory tests
    - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody

Hematology Laboratory Tests

- Basophils
- Mean corpuscular volume
- Eosinophils
- Monocytes
- Hematocrit
- Neutrophils
- Hemoglobin
- Platelet count
- Lymphocytes
- Red blood cell count
- Mean corpuscular hemoglobin
- Total white cell count
- Mean corpuscular hemoglobin concentration

Clinical chemistry(serum or plasma) Laboratory Tests

- Albumin
- Glucose
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase
- Alanine aminotransferase (ALT)
- Magnesium
- Aspartate aminotransferase (AST)
- Potassium
- Bicarbonate
- Sodium
- Calcium
- Total bilirubin
- Chloride
- Total protein
- Creatinine
- Urea or blood urea nitrogen, depending on local practice
- Gamma-glutamyl Transferase (GGT)
- Uric acid

a If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

b At baseline and as clinically indicated

Urinalysis Tests

- Bilirubin
- pH

- Blood
- Protein
- Glucose
- Specific gravity
- Ketones
- Colour and appearance

a Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

Assessments for subjects who have completed nivolumab treatment or have discontinued nivolumab due to toxicity in the absence of confirmed progressive disease are provided in confirmed progressive disease are provided in Table 2 above.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Dose Modification and Toxicity Management

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for nivolumab are in the Dosing Modification and Toxicity Management Guidelines in Appendix B. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which nivolumab should be permanently discontinued (see section 5.4.1 and the Dosing Modification and Toxicity Management Guidelines in Appendix B).

Following the first dose of nivolumab, subsequent administration of nivolumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in APPENDIX B. Dose reductions are not permitted. Based on the mechanism of action of nivolumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix B, Tables 1, 2, and 3 respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Appendix B, Table 1. All toxicities will be graded according to NCI CTCAE v5.0.

6.2 Study Restrictions and Concomitant Treatment

6.2.1 Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 1 highly effective method of contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

• Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal.

• Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

• Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 2. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).
• Nonsterilised males who are sexually active with a female partner of childbearing potential must use use male condom plus spermicide (see Table 1) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 1. Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods
• Hormonal Methods
• Copper T intrauterine device
• Levonorgestrel-releasing intrauterine system (e.g., Mirena®)a
• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant®
• Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing®
• Injection: Medroxyprogesterone injection: e.g. Depo-Provera®
• Combined Pill: Normal and low dose combined oral contraceptive pill
• Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra®
• Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

a This is also considered a hormonal method

6.2.2 Blood donation

Subjects should not donate blood while participating in this study

6.2.3 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Section 6.2.4.

Supportive medication/class of drug:

Usage:

Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as “prohibited,” as listed above

To be administered as prescribed by the Investigator

Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])

Should be used, when necessary, for all patients

Inactivated viruses, such as those in the influenza vaccine

Permitted

6.2.4 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.
1. Any investigational anticancer therapy other than the protocol specified therapies
2. mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study.
3. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, other than the protocol specified therapy. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
5. Live attenuated vaccines within 30 days of nivolumab dosing (i.e., 30 days prior to the first dose, during treatment with nivolumab and for 30 days post discontinuation of nivolumab). Inactivated viruses, such as those in the influenza vaccine, are permitted.
6. EGFR TKIs should not be given concomitantly and should be used with caution in the 90 days post last dose of nivolumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when other immunotherapy has been given concomitantly.
7. Herbal and natural remedies which may have immune-modulating effects.

7.0 ASSESSMENT OF SAFETY

7.1. Safety Parameters

7.1.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1) defines an AE as:
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.
Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.
Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.
The term AE is used to include both serious and non-serious AEs.

7.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:
• Results in death
• Is immediately life-threatening
• Requires in-patient hospitalization or prolongation of existing hospitalization

• Results in persistent or significant disability or incapacity
• Is a congenital abnormality or birth defect in offspring of the subject
• Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Bristol Myers Squibb (information below).

7.1.3 Definition of adverse events of special interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to Bristol Myers Squibb. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for nivolumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with nivolumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with nivolumab include:
• Diarrhea/Colitis and intestinal perforation
• Pneumonitis/ILD
• Hepatitis/transaminase increases
• Neuropathy / neuromuscular toxicity (Guillain-Barré, and myasthenia gravis)
• Endocrinopathy (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, , hyper- and hypothyroidism, and type I diabetes mellitus),
• Rash/Dermatitis
• Nephritis/blood creatinine increases
• Pancreatitis (serum lipase and amylase increases)
• Myocarditis
• Myositis/Polymyositis
• Intestinal perforations

Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to:
• Pericarditis
• Sarcoidosis
• Uveitis
• Other events involving the eye and skin
• Hematological events
• Rheumatological events
• Vasculitis
• Non-infectious meningitis
• Non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.
Further information on these risks (e.g. presenting symptoms) can be found in the current version of the nivolumab Investigator Brochure.

7.1.4 Pneumonitis

Adverse events of pneumonitis are of interest, as pneumonitis has been reported with anti-PD-1 MAbs 51. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.
Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Appendix B, Table 1.

7.1.5 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-L1 and anti-PD-1 therapy 51, 69. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.
Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion related reactions are outlined in Appendix B, Table 1.

7.1.6 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies 69. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.
Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix B, Table 1.
Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs, These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

Criteria for Hy's Law (FDA Guidance 2009)

• The drug causes hepatocellular injury, generally shown by a higher incidence of 3 fold or greater elevations above the ULN of ALT or AST
• Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
• No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

7.1.7 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when anti-PD1 therapy is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead

to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving nivolumab are provided in Table 1.

7.1.8 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Table 1.

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7.1.9 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Table 1.

7.1.10 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 1.

7.1.11 Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc). Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 1.

7.1.12 Radiation Risks

This is a non-ablative subclinical radiation dose that is expected to be associated with extremely low risk.

7.2 Assessment of safety parameters

7.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:

• Definite – The AE is clearly related to the study treatment.
• Probable – The AE is likely related to the study treatment.
• Possible – The AE may be related to the study treatment.
• Unlikely – The AE is doubtfully related to the study treatment.
• Unrelated – The AE is clearly NOT related to the study treatment.

7.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to Bristol Myers Squibb Patient Safety.

The following variables will be collected for each AE:

• AE (verbatim)
• The date when the AE started and stopped
• Changes in NCI CTCAE grade and the maximum CTC grade attained
• Whether the AE is serious or not
• Investigator causality rating against nivolumab (yes or no)
• Action taken with regard to nivolumab

• Outcome
In addition, the following variables will be collected for SAEs as applicable:
• Date AE met criteria for serious AE
• Date Investigator became aware of serious AE
• Reason AE is serious
• Date of hospitalization
• Date of discharge
• Probable cause of death
• Date of death
• Autopsy performed
• Description of AE
• Causality assessment in relation to Study procedure(s

7.3.1 Study recording period and follow-up for AEs and SAEs

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of nivolumab or initiation of new anti-cancer therapy, whichever occurs first). During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.
The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.
Bristol Myers Squibb retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.3.2 Serious Adverse Event (SAE) Reporting

7.3.2.1 Reporting of Serious Adverse Event to Lead Investigator/Coordinating Center

All serious adverse events and all adverse events that have been specified as Events of Special Interest occurring on this study require expedited reporting to the Montefiore Medical Center/Albert Einstein College of Medicine (Coordinating Center). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, Lead Study Coordinator and the Data Safety Monitoring Committee at Albert Einstein College of Medicine within 24 hours of first awareness of the event.

Study Lead Investigator: Dr. Brendon Stiles- brstiles@montefiore.org

Data Safety Monitoring Committee- dsmc@montefiore.org
Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.
All SAEs should be reported to the local IRBs per current local institutional standards.

The Coordinating Center will disseminate information regarding SAEs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and BMS, as appropriate (outlined below).

7.3.2.2 Reporting of Serious Adverse Event to BMS

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**. If applicable,** SAEs must be collected that relate to any follow-up protocol-specified procedure (eg, a follow-up skin biopsy).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are 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.
- 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.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved study specifi/institutional SAE form.

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.

PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The study supporter-Investigator must immediately notify **Worldwide.Safety@bms.com** of this event and complete one of the following forms **within 24 hours of awareness** of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with **SAE reporting procedures.**

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the **CIOMS, MedWatch, BMS**

Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for study supporter-Investigator or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

7.3.3 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 hours of investigator notification of the event.
- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet will be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:
https://einsteinmed.edu/administration/institutional-review-board/re-info.aspx

7.3.4 Reporting of SAE to FDA

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The investigator is responsible for informing the IRB of the SAE as per section 7.5.2. The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of nivolumab or until the initiation of alternative anticancer therapy.

The Investigator will inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to Bristol Myers Squibb. A copy of the MedWatch/AdEERs report will be faxed to Bristol Myers Squibb at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to Bristol Myers Squibb at the same time.

* A *cover page* should accompany the *MedWatch/AdEERs* form indicating the following:
• "Notification from an Investigator Sponsored Study"
• The investigator IND number assigned by the FDA
• The investigator's name and address
• The trial name/title and Bristol Myers Squibb ISS reference number (ESR-##-#####)
* The investigator will also indicate, either in the SAE report or the cover page, the *causality* of events *in relation to all study medications* and if the SAE is *related to disease progression*, as determined by the principal investigator.
* *Send SAE report and accompanying cover page by way of email to* Bristol Myers Squibb *designated mailbox.*

If a non-serious AE becomes serious, this and other relevant follow-up information will also be provided to Bristol Myers Squibb and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to Bristol Myers Squibb preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

7.3.5 Reporting of deaths

All deaths that occur during the study or within the protocol-defined 90-day post-last dose of nivolumab safety follow-up period will be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death will be reported to as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE. .
- Deaths that occur following the protocol-defined 90-day post-last-dose of nivolumab safety follow-up period will be documented, but will not be reported as an SAE.

7.3.6 Other events requiring reporting

Reporting Abnormal Lab Values

Lab abnormalities should not be considered SAEs unless they meet the following criteria:

Definition of SAE

1. **Results in death**
2. **Is immediately life-threatening**
3. **Requires in-patient hospitalization or prolongation of existing hospitalization**
4. **Results in persistent or significant disability or incapacity**
5. **Is a congenital abnormality or birth defect in offspring of the subject**
6. **Is an important medical event that may jeopardize the patient or may require medical intervention to**

Additionally, all abnormal lab values will be reported in the AE log if deemed clinically significant by treating physician and be documented appropriately. ”

7.3.7 Overdose

An overdose is defined as a subject receiving a dose of nivolumab in excess of that specified in the Investigator’s Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with nivolumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to Bristol Myers Squibb Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE will also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and will be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of nivolumab. The investigator will use clinical judgment to treat any overdose.

7.3.8 Hepatic function abnormality

Hepatic function abnormality (as defined section 7.1.6) in a study subject, with or without associated clinical manifestations, is required to be reported as “hepatic function abnormal” *within 24 hours of knowledge of the event* to Bristol Myers Squibb Patient Safety using the designated Safety e-mailbox, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries will be initiated by the Investigator without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by Bristol Myers Squibb.

7.3.9 Pregnancy

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate Bristol Myers Squibb representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Bristol Myers Squibb representative will work with the Investigator to ensure that all relevant information is provided to the Bristol Myers Squibb Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.10 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of nivolumab monotherapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator will obtain the consent of the patient's partner. An IRB approved consent will be obtained prior to use.

7.4 Data Safety Monitoring Plan

Subjects will be carefully monitored and evaluated for adverse events by history, physical examination, and laboratory investigations prior to their scheduled nivolumab infusion and on a monthly basis after surgical resection for 4 months. All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected, and caused subject harm, will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during monthly meetings.

If there are 3 or more postoperative deaths in the first 20 patients this would be considered outside of our historical control, and thus the study would be stopped. The Albert Einstein College of Medicine/Albert Einstein Cancer Center Data Safety Monitoring Committee (DSMC) will perform data and safety monitoring for this study every other month. The DSMC will review interim data to evaluate research subject safety, rates of accrual, and efficacy of the experimental intervention. After each evaluation, the Board will provide the principal investigator with recommendations for protocol modification, continuation, or termination.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Investigational Agent can be found in Section 7.1.

8.1 Investigational Agent

8.1.1 Nivolumab

Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Nivolumab is produced from cell culture using a CHO cell line. The physical and chemical properties of nivolumab drug substance are provided in Table 8.1.1-1.

Table 8.1.1-1: Physical and Chemical Properties of Nivolumab Drug Substance

BMS Number	BMS-936558-01
Other Names	nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

8.1.2 Formulation/packaging/storage

Formulation

The nivolumab (Opdivo®) dosage forms are provided in Table 8.2.1-1. The drug products are sterile, non-pyrogenic, single-use, isotonic aqueous solutions for intravenous (IV) infusion. Nivolumab Injection, 40 mg/Vial (10 mg/mL), 100 mg/Vial (10 mg/mL), 120 mg/Vial (10 mg/ml), and 240 mg/Vial (10 mg/mL) are also referred to as nivolumab injection.

Drug Product	**Nivolumab Injection**			
Strength	40mg/vial	100mg/vial	120mg/vial[a b]	240 mg/vial
Appearance	Clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates			
Concentration	10 mg/mL			
Vial Fill[c]	4.7 mL	10.7 mL /10.5 mL[a]	12.6 mL[a]	25.0 mL /24.6 mL[a]
Vial Size	10cc	10cc	25cc[a]	25cc/30cc[a]
Components	Nivolumab, sodium citrate dihydrate, sodium chloride, mannitol, pentetic acid[d], polysorbate 80, and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment.			
Solution pH	5.5-6.5			
Container Closure System	Type I flint glass vials closed with fluoropolymer film-laminated rubber stoppers, and sealed with aluminum seals			

[a] Information on ONO drug product
[b] 120 mg formulation is available for use in country-specific markets only30
[c] All of the drug products include an overfill to account for vial, needle, and syringe holdup
[d] Also referred to as diethylenetriaminepentaacetic acid

Storage

Nivolumab Injection

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

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

The administration of nivolumab infusion must be completed within 24 hours of preparation. If

not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

8.1.3 Study drug preparation

Preparation of nivolumab deministration with an IV bag

Nivolumab Injection

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (eg, polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection or 5% dextrose injection to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kg of patient weight.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection will be provided to the clinical site. Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, and glass bottles.

Nivolumab hold and infusion times

8.1.4 Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix B.

8.1.5 Agent Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from study supporter on a Drug Accountability Record Form (DARF).

9.0 MEASUREMENT OF EFFECT

9.1 Assessment of disease-free survival

All patients will be followed in our thoracic oncology follow-up clinic for disease recurrence using history, physical examination and CT scanning every 6 months for 2 year, then yearly thereafter till year 5. This follow-up protocol represents our institutional standard of care. Recurrence will be histologically or cytologically confirmed whenever possible. For the purpose of this trial DFS is defined as confirmed disease recurrence or death from any cause.

9.2 Assessment of clinical response.

All patients will have pre-treatment and post-treatment standard imaging including computerized tomography scan (CT scan) to determine disease stage and assess response to therapy. Independent radiologists blinded to treatment allocation will assess tumor shrinkage using conventional RECIST criteria 1.1.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

9.3 Assessment of pathological response

Major Pathologic Response (MPR): ≤10% residual viable tumor in the resected specimen on histopathological examination.

Complete Pathological Response (CPR): The absence of tumor cells in the resected specimen on histopathological examination.

10.0 DATA REPORTING / REGULATORY CONSIDERATIONS

10.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled patients.

10.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by Montefiore-Einstein. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on institution-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. BMS will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

10.3 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

11. STATISTICAL CONSIDERATIONS

11.1 Sample size The primary aim of this study is to determine whether non-ablative SBRT at a dose of 8 Gyx3 given concurrently with neoadjuvant nivolumab/chemotherapy will increase the complete pathologic response (CPR) rate. The CPR rate in the Cornell study of low dose SBRT + durvalumab was 26%, but it should be noted that this was with durvalumab alone + SBRT rather than with combined therapy. The addition of chemotherapy to neoadjuvant IO has markedly increased CPR/MPR in several single arm studies compared to IO alone. We are thus predicting that the >2-fold increase in CPR seen from the addition of SBRT in the Cornell study will also be realized in this study. The baseline rate of CPR with nivolumab/chemotherapy is estimated from CM816.

Sample size justification: We hypothesize that the CPR rate will be 25% in Arm 1 (nivolumab/ chemotherapy alone) and that the CPR rate will be 55% in Arm 2 (SBRT+nivolumab/chemotherapy). Under the above assumption, a group sample size of 24 in each arm (n=48) will achieve an 81.1% power to detect a difference in group proportion of 30% using a two-sided Z test with pooled variance. As this is a screening phase II design, the type I error rate is targeted at 20%. We anticipate approximately 7.5% drop-out rate among our patient population; thus we will inflate the sample size and recruit 26 patients per arm (52 in total)

11.2 Analysis Plan for Endpoints

11.2.1 Primary Endpoint

The study's primary endpoint is complete pathological response (CPR) observed after neoadjuvant therapy and surgical resection. We will summarize the CPR rate proportion along with 95% confidence intervals for each arm. The difference in CPR rate will be assessed using the stratified Cochran Mantel Haenszel (CMH) test or a stratified CMH exact test. Multivariable stratified logistic regression will examine the association between the intervention groups and CPR rate adjusting for covariates.

11.2.2 Secondary Endpoints

- For the secondary endpoint, major pathologic response (MPR) will be defined as ≤ 10% residual viable tumor cells in the primary tumor and resected lymph nodes. MPR rate and corresponding 95% Clopper-Pearson confidence intervals will be calculated for each treatment arm. Exploratory comparisons of MPR rates across study arms will be performed utilizing stratified Cochran Mantel-Haenzsel chi-square or exact tests. Multivariable stratified logistic regression will be used for assessing the effects of the intervention on MPR adjusting for potential confounders.
- The time to event endpoints, including event-free survival (EFS), will be assessed using survival analysis. The failure time probabilities will be assessed using Kaplan-Meir product limit estimators with corresponding 95% confidence intervals. Comparison of failure time events between the interventions will be evaluated using the stratified log-rank test, and covariate-adjusted effects will be assessed using stratified Cox regression models.

11.2.3 Exploratory Aims:

- As an exploratory Aim, we will evaluate pathologic downstaging of biopsy confirmed lymph nodes. Although absolute rates of pathologic downstaging (versus downstaging from clinically staged mediastinal lymph nodes) in neoadjuvant immunotherapy trials are difficult to determine, the rate of nodal downstaging in a small cohort of patients with pathologically confirmed nodes in the neoadjuvant trial of nivolumab plus SBRT reported by Altorki et al. was 66% vs. 14% for nivolumab alone. We expect that rates will exceed 25% in the nivolumab/chemotherapy arm and that they will exceed 50% in the SBRT plus nivolumab/chemotherapy arm.
- We will also evaluate 2-year DFS and OS between the two arms. We anticipate that the addition of SBRT will extend the 2-year DFS and ultimately improve OS. This comparison will be for exploratory purposes only (this comparison will not be statistically powered to detect specific differences between the two arms).
- An additional secondary aim is to determine the incidence of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. We will also assess the surgical safety of 3 cycles of preoperative nivolumab and chemotherapy with and without radiation and to compare the incidence of surgery related adverse events. Surgical metrics including operative time, rates of minimally invasive versus open thoracotomy procedures, of conversions from minimally invasive approach to open approach, and lobectomy versus pneumonectomy will be compared between arms.
- We will determine whether the addition of non-ablative SBRT is associated with higher rates of ctDNA clearance in blood samples taken post-treatment and whether ctDNA clearance is associated with CPR. In CheckMate 816, the rate of ctDNA clearance in the Nivo/chemo arm

was 56%. We anticipate higher rates with the addition of SBRT and expect an association with CPR.

- Finally, we will undertake several correlative translational studies to assess for pre-operative predictors of CPR including PD-L1 expression, tumor immunophenotype by multiplex immunofluorescence, whole tumor gene expression, and blood-based gene expression panels.

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APPENDIX A
NIVOLUMAB DOSE CALCULATIONS
Nivolumab Dosing
Please ensure the correct dose level is used. Below is an example for a 20 mg/kg weight-based dose
Example:

APPENDIX B
DOSING MODIFICATIONS AND TOXICITY MANAGEMENT GUIDELINES
Tables 1, 2 and 3
Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions
General Considerations regarding Immune-Mediated Reactions Dose Modifications Toxicity Management
Immune-related
Adverse Events
(Overall
Management For
toxicities not noted
below)
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0 (unless indicated otherwise.)
In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE)
• Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing.
It is recommended that management of immune-mediated Adverse Events (imAEs) follow the guidelines presented in this table
• It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted specifically in these

guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
• For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone 1-2mg/kg/day PO or IV equivalent
• Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even
Grade 1 No dose modification
Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
•Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper
Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.
if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.
• If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (> 28 days of taper)
• More potent immunosuppressives such as TNF inhibitors (e.g. infliximab; also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.
• With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.
• Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient
Grade 3
Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below
Grade 4
Permanently discontinue study drug/study regimen
Note: For asymptomatic amylase or lipase levels of >2.0×ULN, hold study drug/regimen and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper
Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type1 diabetes mellitus).

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Pneumonitis//Interstitial Lung Disease (ILD)
Grade of Pneumonitis (CTCAE version 5.0)
General Guidance
• Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below
• Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
Grade 1
(Asymptomatic, clinical or diagnostic observations only, intervention not indicated)
No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies
For Grade 1 (Radiographic Changes Only)
• Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated
• Consider Pulmonary and Infectious Disease consults.
Grade 2
(Symptomatic, medical intervention indicated, limiting instrumental ADL)
Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
• If toxicity improves to < Grade 1 then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.
For Grade 2 (Mild to Moderate New Symptoms)
• Monitor symptoms daily and consider hospitalization
• Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent)
• Reimaging as clinically indicated
• If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started
• If still no improvement within 3-5 days despite IV

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab

• Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a
• Consider Pulmonary and Infectious Disease Consults
• Consider as necessary discussing with study physician
Grade 3 or 4
(Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated;
Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])
Permanently discontinue study drug/study regimen
For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening
• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent
• Obtain Pulmonary and Infectious Disease consults; consult, as necessary, discussing with study physician.
• Hospitalize the patient
• Supportive Care (oxygen, etc.)
• If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
• Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)i
Diarrhea/ Colitis
Large intestine perforation/Intestine perforation
Grade of Diarrhea (CTCAE version 5.0)
General Guidance
- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus)
- When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.)
- Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event, including perforation.
- Use analgesics carefully; they can mask symptoms of perforation and peritonitis

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 1 Diarrhea: (stool frequency of <4 over baseline per day)
(Colitis: asymptomatic; clinical or diagnostic observations only)

No dose modification
For Grade 1 diarrhea :
- Close monitoring for worsening symptoms
- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
Grade 2 Diarrhea: (stool frequency of 4-6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)
(Perforation: symptomatic; medical intervention indicated*)
Hold study drug/study regimen until resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
• If toxicity improves to < Grade 1 then study drug/study regimen can be resumed after completion of steroid taper.
For Grade 2 diarrhea:
- Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide
- Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent
- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.
- If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
* "medical intervention" is not invasive
immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks1). . **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab
- Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3 to 4 days.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 3 or 4 diarrhea
(Grade 3 Diarrhea: Stool frequency of ≥7 over baseline per day;
Grade 4 Diarrhea: life threatening consequences)
(Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs;
Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms,
Grade 3
Permanently discontinue study drug/study regimen- for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper.

Grade 4
Permanently discontinue
study drug/study regimen.
For Grade 3 or 4 diarrhea:
- Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent
- Monitor stool frequency and volume and maintain hydration
- Urgent GI consult and imaging and/or colonoscopy as appropriate
- If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.
- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections).a

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated)
*This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective
Hepatitis (Elevated LFTs)
Infliximab should not be used for management of Immune Related Hepatitis
Any Elevations in AST, ALT or TB as Described Below
For Any Elevations Described:
- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin
- Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
AST or ALT > ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal;
• No dose modifications.
If it worsens, then treat as described for elevations in the row below.
- Continue LFT monitoring per protocol

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
and/or TB > ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal
AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5- 3.0×baseline if baseline abnormal
• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal.
• If toxicity worsens, then treat as described for elevation in the row below.
If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.
Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved.

- If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with study physician.
- If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day.
- If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).a Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a
AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal
For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal:
• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal
• Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5× ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of
− Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.
- If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
- Request Hepatology consult, and perform abdominal workup and imaging as appropriate.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
steroid taper.
• Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days
For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study drug/study regimen.
Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.b

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)
Grade of Elevated Serum Creatinine (CTCAE version 5.0)
Any Grade
General Guidance
- Consult with Nephrologist
- Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)
- Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]
No dose modification
For Grade 1 elevated creatinine:
- Monitor serum creatinine weekly and any accompanying symptom
• If creatinine returns to baseline, resume its regular monitoring per study protocol.
• If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4
- Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]
Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline
• If toxicity worsens then treat as Grade 3 or Grade 4
• If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper
For Grade 2 elevated creatinine:
- Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
- Carefully monitor serum creatinine every 2-3 days and as clinically warranted
- Consult Nephrologist and consider renal biopsy if clinically indicated
- If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent
- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started.
- Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.
- When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 3 or 4
(Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN)
(Grade 4: Serum Creatinine > 6.0 X ULN)
Permanently discontinue study drug/study regimen
- Carefully monitor serum creatinine on daily basis
- Consult Nephrologist and consider renal biopsy if clinically indicated
- Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent
- If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.
- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections.
Rash or Dermatitis
(including Pemphigoid)
Any Grade
(Please refer to NCICTCAE version 5.0 for definition of severity/grade depending on type of skin rash)
General Guidance
For Any Grade:
- Monitor for signs and symptoms of dermatitis (rash and pruritus).
- IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 1
No dose modification
For Grade 1:
- Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
Grade 2
For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline
• If toxicity worsens then treat as Grade 3
• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper
For Grade 2 :
- Obtain Dermatology consult
- Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
- Consider moderate-strength topical steroid

- If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent
- Consider skin biopsy if persistent for >1-2 weeks or recurs
Grade 3
Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline
If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue
For Grade 3 or 4:
- Consult Dermatology
- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent
- Consider hospitalization
- Monitor extent of rash [Rule of Nines]

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Study drug/study regimen
- Consider skin biopsy (preferably more than 1) as clinically feasible.
- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
- Consider, as necessary, discussing with Study Physician
Grade 4
Permanently discontinue study drug/study regimen
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency.): exocrine event of amylase/lipase increased also included in this section)
Any Grade
(Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity)
General Guidance
- Consider consulting an Endocrinologist for endocrine events.
- Consider, as necessary, discussing with study physician.
- Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria hypotension and weakness.
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)
- Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant and related labs (e.g., blood glucose and ketone levels, HgA1c).
- For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management

- If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1
(Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade 1)
No dose modification
For Grade 1: (including those with asymptomatic TSH elevation)
- Monitor patient with appropriate endocrine function tests.
- For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency).
- If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
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Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 2
(Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity 2)
For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus hold study drug/study regimen dose until subject is clinically stable
• If toxicity worsens then treat as Grade 3 or Grade 4
•
Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g. adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:
1) the event stabilizes and is controlled
2)) the patient is clinically stable as per Investigator or treating physician's clinical judgement,
3) Doses of prednisone are at less than or equal to 10mg/day or equivalent.
For Grade 2: (including those with symptomatic endocrinopathy)
- Consult endocrinologist to guide evaluation of endocrine function, and as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan
- For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). -
- Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
- For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management

Grade 3 or 4
(Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity 3 or 4)
For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled
Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper
Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:
1. The event stabilizes and is controlled.
2. The patient is clinically stable as per investigator or treating physician's clinical judgement.
3. Doses of prednisone are ≤10 mg/day or equivalent.
For Grade 3 or 4:
- Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended.
- For all patients with abnormal endocrine work up, except those with isolated hypothyroidism
- Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent
- as well as relevant hormone replacement (e.g. hydrocortisone, sex hormones)
- For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity
- Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.
- Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.
- Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PJP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.
Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)
Grade of Neurotoxicity
Depending on the type of neurotoxicity , refer to NCI CTCAE version 5.0 for defining the CTC grade/severity
Any Grade
General Guidance
- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.)
- Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness)
- Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations)

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management

- Perform symptomatic treatment with Neurology consult as appropriate
Grade 1
No dose modifications
See "Any Grade" recommendations above.
Grade 2
• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1
• For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1.
o If toxicity worsens then treat as Grade 3 or Grade 4
• Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper
- Consider, as necessary, discussing with the study physician
- Obtain Neurology Consult
- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)
- Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent
- If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
Grade 3
• Hold Study drug/study regimen dose until resolution to ≤ Grade 1
• Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days.
For Grade 3 or 4:
- Consider, as necessary, discussing with study physician
- Obtain Neurology Consult
- Consider hospitalization
- Promptly initiate empiric IV methylprednisolone 1 to 2

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 4
• Permanently discontinue study drug/study regimen
mg/kg/day or equivalent
- If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG)
- Once stable, gradually taper steroids over ≥28 days
Peripheral neuromotor syndromes
(such as Guillain-Barre and myasthenia gravis)
General Guidance
- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability
- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due

to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult
- Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation
- It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
Grade 1
No dose modification
- Consider, as necessary, discussing with the study physician
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above
- Obtain a Neurology consult
Grade 2
Hold study drug/study regimen dose until resolution to ≤ Grade 1
Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability
Grade 2
- Consider, as necessary, discussing with the study physician
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above
- Obtain a Neurology Consult
- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)
MYASTHENIA GRAVIS
o Steroids may be successfully used to treat Myasthenia

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.
o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.
o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.
GUILLAIN-BARRE:

o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
Grade 3
Hold study drug/study regimen dose until resolution to ≤ Grade 1
Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability
For severe or life threatening (Grade 3 or 4) events:
- Consider, as necessary, discussing with study physician
- Recommend hospitalization
- Monitor symptoms and obtain Neurology consult
MYASTHENIA GRAVIS
o Steroids may be successfully used to treat Myasthenia

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 4
Permanently discontinue study drug/study regimen
Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist.
o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.
o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.
GUILLAIN-BARRE:
o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
o Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
Myocarditis
Any Grade
Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.
For Any Grade:
− The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.
− Consider, as necessary, discussing with the study physician.
− Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain,

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be

obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.
− Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1
(asymptomatic with laboratory [e.g., BNP] or cardiac imaging abnormalities)
No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to
For Grade 1 (no definitive findings):
-Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 2, 3 or 4
(Grade 2: Symptoms with mild to moderate activity or exertion)
(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))
Grade 0.
-If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. Discontinue study drug/study regimen.
- If Grade 3-4, permanently discontinue study drug/study regimen.
-Consider using steroids if clinical suspicion is high.
For grade 2-4:
− Monitor symptoms daily, hospitalize.
− Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy.
− Supportive care (e.g., oxygen).
− If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
− Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management

Myositis/Polymyositis (“Poly/myositis”)
Any Grade
General Guidance
For Any Grade:
− Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.
− If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation.
− Consider, as necessary, discussing with the study physician.
− Initial work-up should include clinical evaluation,

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Grade 1
(mild pain)
Grade 2
(moderate pain associated with
For Grade 1:
-No dose modifications.
For Grade 2:
Hold study drug/study regimen dose until resolution to Grade ≤1.
creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
For Grade 1:
−Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.
−Consider Neurology consult.
−Consider, as necessary, discussing with the study physician.
For Grade 2:
−Monitor symptoms daily and consider hospitalization.
−Obtain Neurology consult, and initiate evaluation.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)

Dose Modifications
Toxicity Management
weakness; pain limiting instrumental activities of daily living [ADLs])
Grade 3 or 4
(pain associated with severe weakness; limiting self-care ADLs)
-Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.
For Grade 3:
Hold study drug/study regimen dose until resolution to Grade ≤1.
Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are
−Consider, as necessary, discussing with the study physician.
−If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant
−If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day
−If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
−Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).
For Grade 3 or 4 (severe or life-threatening events):
−Monitor symptoms closely; recommend hospitalization.
−Obtain Neurology consult, and complete full evaluation.
−Consider, as necessary, discussing with the study physician.
−Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
signs of respiratory insufficiency.
For Grade 4:
-Permanently discontinue study drug/study regimen.
consultant.
−If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
−Consider whether patient may require IV IG, plasmapheresis.
−Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Nivolumab Monotherapy
Table 2- Infusion-Related Reactions
Severity Grade of the Event (NCI CTCAE version 5.0)
Dose Modifications
Toxicity Management
Any Grade
General Guidance
- Management per institutional standard at the discretion of investigator
- Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1
The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event
For Grade 1 or Grade 2:
- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator
- Consider premedication per institutional standard prior to subsequent doses
- Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
Grade 2
The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event
Subsequent infusions may be given at 50% of the initial infusion rate
Grade 3/4
Permanently discontinue study drug/study regimen
For Grade 3 or 4:
Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)
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Abbreviations:
AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine
aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD
= interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer
Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating
hormone; ULN = upper limit of normal.
Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for
Nivolumab Monotherapy
Table 3- Non-immune Mediated Reactions
Severity Grade of
the Event (NCI

CTCAE version
5.0)
Dose Modification Toxicity Management
Any Grade Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.
Treat accordingly as per institutional
standard
1 No dose adjustment Treat accordingly as per institutional
standard
2 Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline Treat accordingly as per institutional
standard
3 Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline
For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen
Treat accordingly as per institutional
standard
4 Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the study supporter)
Treat accordingly as per institutional
standard

Human Research Protections Program
Immediate Report Form
The Immediate Reporting Policy that governs what you must report using this form is available at the following web address: http://
The policy spans 5 categories: Adverse Events/Unexpected Adverse Device Effects (Section A of this form), Other Risk Reporting (Section B of this form), Protocol Deviation Reporting (Section C of this form) and Other Compliance Reporting (Section D of this form).
If you have any questions, please email
.
DIRECTIONS:
(a) Fill out questions 1 through 8 on this page.
(b) Then choose the section on this form that corresponds to the type of Immediate Report you are making. Any given section you choose will have only 1 to 7 questions.
(c) Create a PDF of this form and attach the most current AECM/AECC IRB consent document and any supplemental information.
(d) Sign this form with Principal Investigator signature on the last page and send to
NOTE:
• If you are using the Albert Einstein College of Medicine Data Safety Monitoring Committee (AECM/AECC DSMC) you must also CC your Immediate Report to
• If your protocol is subject to the requirements of the Institutional Biosafety Committee (IBC), you must also CC your Immediate Report to
1. Principal Investigator:
2. Protocol #:
3. Protocol Title:
4. Brief One Sentence Description of Report (**This will be used to reference this specific submission in all IRB correspondence about this Immediate Report**):

5. Status of Protocol at AECM/AECC Site Open Open, Closed to Subject Accrual Open, Data Analysis Only
6. Funding Source:
7. Does this protocol involve use of FDA-regulated product(s) including those that are FDA-approved? Yes No
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a. If yes, is this protocol conducted under an IND or IDE? Yes No
b. If yes, name IND or IDE study supporter:
8. Check (and email this submission to) all that apply: I use the: AECM/AECC Data Safety Monitoring Committee (AECM/AECC DSMC)
AECM/AECC Institutional Biosafety Committee (IBC) Clinical and Translational Science Center (CTSC)

A: ADVERSE EVENT REPORTING / UNANTICIPATED ADVERSE DEVICE EFFECTS

Tip: The goal of this section is to capture emergent risk information that has an impact on the rights and welfare of AECM/AECC subjects and may also require compliance management.

1. I am reporting (check all that apply):

Adverse Event that meets all 3 conditions as outlined in Section I(A) of the Immediate Reporting Policy
Adverse Event that requirements for reporting and a death or serious injury due to a defect of a Humanitarian Use Device, as outlined in Section I(C) of the Immediate Reporting Policy
Unanticipated adverse device effect as outlined in Section II(A) of the Immediate Reporting Policy.
Describe the adverse event, its cause, and indicate any actions taken to date at the AECM/AECC site to protect the rights and welfare of AECM/AECC research subjects. Provide as much detail as possible. If the PI or any committee/board determines that the Immediate Report requires an amendment to the protocol or consent, the PI has 30 days from the date of making the Immediate Report (or release of the study supporter amendment) to submit a protocol amendment to the IRB. If this requirement cannot be met, a request for an extension must be made.

1. Please explain whether you believe this adverse event suggests that the research places AECM/AECC subjects at a greater risk of harm than was previously known or recognized. If so, include what additional action you intend to take in your management of this change in risk. E.g., Documented contact with subjects by the PI or medically qualified co-I; amendment to protocol or consent).

2. Name any agencies or entities (E.g., FDA, NIH, study supporter, DSMB, etc.) that have been notified of this adverse event.

B: OTHER RISK REPORTING

Tip: The goal of this section is to capture emergent risk information that has an impact on the rights and welfare of AECM/AECC subjects. If none of the below checkboxes apply, submit an acknowledgment submission instead of an Immediate Report.

1. I am reporting (check all that apply):

An interim analysis, safety monitoring report, publication in the literature, or revised Investigator Brochure that indicates an increase in the frequency or magnitude of a given harm, uncovers a new risk, or provides more information about the benefits of the human research. **(PLEASE ATTACH THE ADDITIONAL DOCUMENTATION)**
Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in the human research protocol.
Clinical Hold, Enrollment Hold (excluding planned holds for interim analysis), or Study Termination due to Emergent Risk Information
Revised 2-2017 3
Complaint of a participant that indicates participants or others might be at increased risk of harm or at risk of a new harm.
2. Please summarize the information and how you intend to manage the new risk posed to AECM/AECC research participants. Include any actions taken to date.

C: PROTOCOL DEVIATIONS

Tip: The study supporter and the IRB are separate and distinct entities with different protocol deviation reporting requirements. Please consult with your study supporter to find out what protocol deviations you must submit to your study supporter. This form is meant to capture protocol deviations that must be reported to the IRB. Note that, i*f AECM/AECC is the lead/coordinating site, then protocol deviation reports submitted from other sites must be submitted to the AECM/AECC IRB.*

1. I am reporting (check all that apply):

Protocol deviation that was made in order to eliminate an apparent immediate hazard to participants.
Breach of Confidentiality
Protocol deviation that represents a failure to follow the protocol or IRB policies and determinations due to the action or inaction of the investigator or research staff. (Exception: Rescheduling of research appointments due to holidays, vacations, accommodation of research subject, etc.) which meets both of the following conditions:
a. The deviation has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject's willingness to participate in the study **AND**
b. The deviation places WCM subjects **at greater risk of harm** (including physical, psychological, economic or social harm).
2. Did this deviation occur at an external site (non-AECM/AECC research site for which AECM/AECC is the lead/coordinating site)?
No Yes, answer (a)
a) What is the status of the research protocol at the non-AECM/AECC research site?
Open Open, Closed to Subject Accrual Open, Data Analysis Only
3. Date the Protocol Deviation Occurred:
4. Date the AECM/AECC PI was notified:
5. Describe the protocol deviation and clearly state how this protocol deviation differs from what the IRB-approved protocol and/or IRB policy allows. Include why the deviation occurred. If the deviation occurred because of an error, please assess the root cause of that error.
6. Describe what actions have been taken to date to ensure the rights and welfare of the participant(s).
7. What preventative actions have been taken to ensure this deviation does not reoccur? Note: While some deviations occur due to human error, some represent systemic issues that need to be resolved. If the research staff will be more careful in the future, please help the IRB understand how the research staff will do this.

D: OTHER COMPLIANCE REPORTING

1. I am reporting (check all that apply):

Finding of noncompliance or allegation of noncompliance
Complaint of a participant that cannot be resolved by the research team.
Incarceration of a participant in a protocol not approved to enroll prisoners.
2. Please describe the scenario in detail and indicate any actions taken to date:
AECM/AECC Principal Investigator's Signature _____ Date: _____

IMPORTANT: Before providing your digital signature, combine this form and supporting documents into a single PDF.

Note on dates of receipt: In order to ensure the effective review of emergent risks to research subjects, the IRB cannot honor the received date of Immediate Report submissions with questions left blank or without the information requested. Immediate Reports are considered received as of the date this form is received with all questions on the form answered as instructed.
Certain adverse events and incidents must be immediately reported to Patient Services, Risk Management, and/or the Department of Health. Please refer to the following policies/offices to

determine whether this event qualifies for reporting to any of the aforementioned groups. Risk Management Incident Reporting (x66180): SAEs/Sentinel Events Reporting: