# Consolidative Ipilimumab and Nivolumab with Thoracic Radiotherapy after Platinum Based Chemotherapy for Patients with Extensive-Stage Small Cell Lung Cancer

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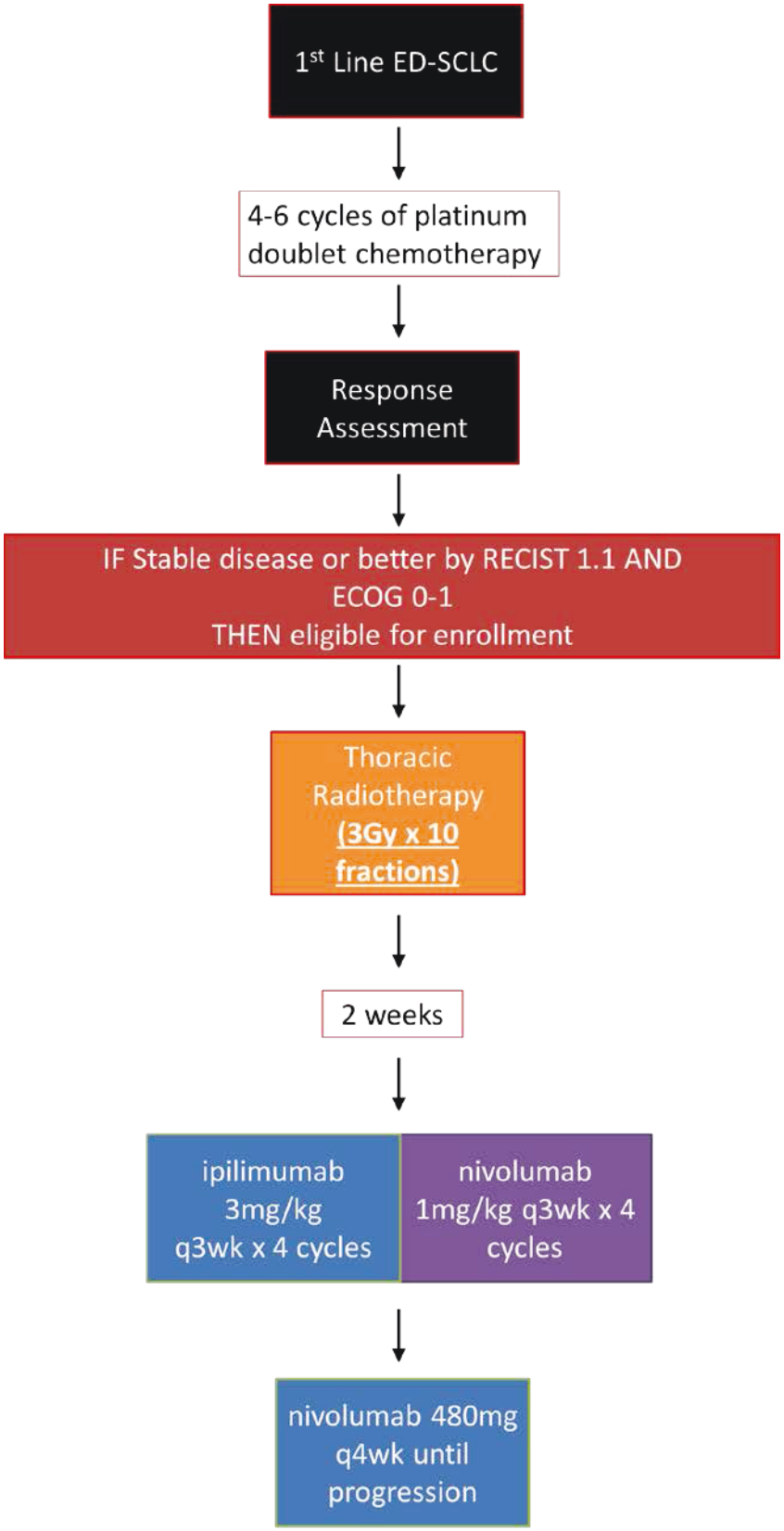
# STUDY SYNOPSIS



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# 1 INTRODUCTION

MCC18914 is a nonrandomized, phase II, single arm, multicenter trial evaluating safety and efficacy of thoracic radiation therapy followed by nivolumab and ipilimumab in participants with Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) who have completed a first-line platinum-based chemotherapy regimen and achieved ongoing complete response (CR), partial response (PR), or stable disease (SD). This study will determine whether nivolumab and ipilimumab delivered 2 weeks following consolidative thoracic radiation therapy demonstrates acceptable toxicity and whether the treatment regimen will improve 6-month progression-free survival (PFS) compared with a similar historical control cohort in this participant population. Additional objectives include further characterization of overall survival, adverse event profile, patterns of failure analysis, and potential predictive biomarkers of response to nivolumab in combination with ipilimumab and thoracic radiation therapy in patients with ED-SCLC.

## 1.1 Study Rationale

### 1.1.1 Rationale for Investigating First-Line Maintenance Therapy in SCLC

SCLC accounts for 15 to 20% of new cases of lung cancer and is associated with poor outcomes. SCLC is traditionally classified as Limited Stage Disease (LD-SCLC: TNM stages I to IIIB) and Extensive Stage Disease (ED-SCLC: TNM stage IV with distant metastases (M1) including malignant pleural effusions). For LD-SCLC, a combined therapeutic approach of radiotherapy, chemotherapy and (rarely) surgery is used with curative intent[1]. Most patients at diagnosis have ED-SCLC and are treated with four to six cycles of etoposide plus platinum-based therapy (EP), which remains the standard chemotherapy regimen for LD- and ED-SCLC[2]. Overall survival (OS) remains poor with median survival for LD-SCLC at 18 to 30 months[3] and for ED-SCLC in the range of 9 to 12 months[4-7]. Despite high initial response rates, in particular in patients with ED-SCLC, the disease does recur or progress rapidly after completion of chemotherapy, with median PFS of only 2-3 months[7, 8]. A Dutch randomized phase III of patients with ED-SCLC treated with thoracic radiation therapy following EP reported a significant improvement in PFS at 6 months (24% vs 7%, HR 0.73) and a significant improvement in 2 year OS (13% vs 3%, p=0.004) with the addition of thoracic radiation therapy[5]. There are no other established standard of care treatments for subjects with ED-SCLC who complete first line therapy with EP and have achieved stable disease or response. In a phase 3 trial of topotecan versus observation, topotecan did not show an OS prolongation for SCLC patients after completion of EP[8]. Recently, sunitinib showed an improved PFS in a Phase 2 trial of sunitinib vs placebo in SCLC patients after completion of EP[7]. Despite the extensive chemotherapy regimens administered to ED-SCLC patients, approximately 75-90% of patients have persistent intrathoracic disease and though consolidative RT alone to the residual thoracic disease can improve time to progression in the thorax, 2 year OS is still only 13% among patients treated with TRT [5]. This underscores the need for more effective treatment options in this devastating malignancy.

Considering the short median OS for patients who have completed first line platinum-based treatment, as well as the even shorter PFS experienced in this disease, new treatments complementary to SCLC standard first-line platinum-based treatment are required.

### 1.1.2 Rationale for Immuno-Oncology Therapeutic Approaches in SCLC

SCLC has classically been associated with immune-mediated paraneoplastic processes, such as cerebellar degeneration, limbic encephalitis and Lambert-Eaton myasthenic syndrome [9]. For example, antibodies generated against human neuronal RNA-binding proteins (e.g. Hu), which are expressed on neurons and SCLC tumors, leads to an encephalomyelitis [10]. Interestingly, SCLC patients that present with these 'early' paraneoplastic syndromes have a more favorable prognosis [11, 12], suggesting that an underlying immune response is being generated against these onconeural antigens.

Proof of an active immune environment in SCLC has been described in a few analyses of patient samples. First, analysis of sixty-four SCLC tumors demonstrated that a wide range of CD45+ cells infiltrated the tumor, an average of 40 immune cells/field, and that high CD45+ counts were associated with a better prognosis [13]. Secondly, a separate study found that various tumor-infiltrating lymphocyte (TIL) subsets were present in SCLC brain metastases and that programmed death ligand 1 (PD-L1) was heterogeneously expressed [14]. Finally, evaluation of peripheral blood cells in 35 SCLC patients demonstrated a high CD4+ effector T cell to T regulatory (Treg) cell ratio in patients with LD-SCLC vs. ED-SCLC [15]. This implies that in some respect, SCLC pathology integrates with the immune response.

Furthermore, SCLC is known to have one of the highest mutational loads [16], which is thought to be a reflection of myriad insults inflicted by carcinogens from smoking. Additionally, comprehensive genomic profiling of SCLC tumors has identified that the vast majority lack functional p53 (90%) and Rb1 (65%) [17]. This universal genetic aberration facilitates poor genomic stability [18], thus perpetuating the generation of tumor-associated antigens (TAAs). Interestingly, recent studies have highlighted that the clinical efficacy of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) blockade in melanoma and non-small cell lung cancer (NSCLC), respectively, are partially driven by the mutational burden of the tumor and the presence of neoantigens [19, 20]. Thus, the high mutational burden in SCLC may facilitate enhanced immune recognition. Though SCLC pathology appears to be intertwined with the immune response and is predisposed by a substantial mutational load, prior evidence indicates that major histocompatibility complex (MHC) surface expression is reduced in SCLC [21, 22], which may preclude robust immune recognition.

These data support the notion that there is an active immune microenvironment within primary and metastatic SCLC lesions. Finally, a phase I/II non-randomized trial (CheckMate 032) evaluated nivolumab with or without ipilimumab in LD-SCLC/ED-SCLC patients that failed platinum-based therapy. This study reported a response rate of 23% at the most efficacious dose level of ipilimumab 3mg/kg and nivolumab 1mg/kg. This study also reported a tolerable safety profile for patients treated at the aforementioned dose level. Considering the immune response seen in SCLC patients, and the results of early phase studies utilizing checkpoint inhibitors nivolumab and ipilimumab in SCLC patients in later treatment lines, it is reasonable to expect that nivolumab and ipilimumab combination therapy are likely to also provide benefit as first line maintenance therapy in SCLC.

### 1.1.3 Rationale for Nivolumab (1 mg/kg)/Ipilimumab (3 mg/kg) Combination in SCLC

In a phase I/II study of nivolumab and nivolumab/ipilimumab for treatment of recurrent SCLC (CA209032), participants who were platinum sensitive or refractory and had progressive disease were enrolled regardless of

tumor PD-L1 status or number of prior chemotherapy regimens [23]. This open-label study randomized participants to nivolumab 3 mg/kg IV every 2 weeks or nivolumab + ipilimumab (1 + 1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) IV every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. The primary objective was objective response rate. Other objectives were safety, PFS, OS and biomarker analysis.

All participants had prior platinum-based first-line treatment and progression after the most recent treatment regimen. Baseline characteristics were typical for a SCLC population with respect to age, smoking history, and gender.

***Safety.*** While the incidence of drug-related adverse events (AEs) in the nivolumab 1 mg kg/ipilimumab 3 mg/kg cohort (79% any grade, 30% grade 3-4) was higher than in the nivolumab monotherapy group (53% any grade, 13% grade 3-4), the treatment discontinuation rate for treatment-related AEs was only 11% (nivolumab 1 mg/kg / ipilimumab 3 mg/kg): 5 patients with diarrhea, myasthenia gravis [subsequently developing complications with fatal outcome], pneumonitis, cardiomyopathy, and 1 patient with hypothyroidism, hyperglycemia, and increased ALT levels).

The most frequent (≥10%, any grade) drug-related AEs were diarrhea, fatigue, rash, pruritus, hypothyroidism, rash maculo-papular, nausea, hyperthyroidism, and increased lipase levels. One treatment-related death in the nivolumab 1 mg/kg / ipilimumab 3 mg/kg cohort occurred. This participant developed myasthenia gravis (reported as grade 4) after treatment start and suffered from complications resulting in death. Limbic encephalitis was reported in 3 participants, which resolved with immunosuppressive treatment in 2 cases. Another participant had a minor response to immunosuppressive treatment and eventually died due to the underlying tumor disease.

***Efficacy***. Patients treated at the recommended phase III dose of ipilimumab 3mg/kg and nivolumab 1mg/kg (n=61) were noted to have an overall response rate (ORR) of 23%, and the disease control rate (CR + PR + SD) was 44%. Objective responses were long lasting, with a median duration of response of 7.7 months in the nivolumab 1mg/ipilimumab 3 mg combination group. The median PFS was 2.6 months (95% CI: 1.4, 4.1) The median OS was 7.7 months (95% CI: 3.6, 18) in the nivolumab 1 mg /ipilimumab 3 mg combination group, which compares favorably with historical controls [8]. There is an ongoing phase III randomized, placebo-controlled study (CA209-451) evaluating PFS and OS among patients with ED-SCLC with at least stable disease after 4 cycles of EP chemotherapy. More than 800 patients are to be randomized to placebo, nivolumab 240 mg delivered every 2 weeks, or ipilimumab 3 mg + nivolumab 1 mg combination therapy for 4 cycles followed by nivolumab 240 mg every 2 weeks until progression. Patients will be carefully monitored on this protocol, and we expect results from our study with comparable inclusion criteria to be available in the coming years.

### 1.1.4 Rationale for Consolidative Thoracic Radiation Therapy

In a phase III study of consolidative thoracic radiation therapy for treatment of patients with ED-SCLC in the first line, participants who had any response to systemic 4-6 cycles of EP chemotherapy were enrolled in a randomized fashion to either no further treatment or to receive a 30-Gy dose of radiation delivered in 10 daily fractions to any residual intrathoracic disease including all initially involved hilar and mediastinal lymph node stations[5]. All patients also received prophylactic cranial irradiation as part of the study protocol. Baseline characteristics were typical for a SCLC population with respect to age, smoking history, and gender.

***Safety***. Consolidative thoracic radiation therapy was well tolerated in the above study. Ninety-five percent of patients completed the protocol-specified radiation therapy without interruption, with only 1 patient discontinuing treatment. The rate of grade 3 and higher toxic effects was only 10.5% compared with 7.2% in the control arm that received no thoracic radiation therapy. The incidence of grade 3 dyspnea or cough was only 1.2% in the thoracic radiation therapy group.

**Efficacy.** The multi-center study from Slotman et al. described above enrolled 498 patients. The study reported a significant improvement in PFS at 6 months (24% vs 7%, HR 0.73) and a significant improvement in 2-year OS (13% vs 3%, p=0.004) with the addition of TRT. Another randomized study by Jeremic et al., which included 206 patients with ED-SCLC who were treated with 3 cycles of EP, reported complete response at distant sites and at least a partial response in the chest [6]. Patients were randomized to thoracic radiation therapy with low-dose chemotherapy versus chemotherapy alone for 4 additional cycles. Patients who received thoracic radiation therapy reported significantly increased OS compared with chemotherapy alone (median 17 vs 11 months, 5-year OS of 9% vs 4%).

### 1.1.5 Rationale for Omission of Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) remains controversial for patients with ED-SCLC. One randomized controlled study evaluating the efficacy of PCI by Slotman et al. demonstrated a survival benefit with treatment. In that study, the hazard ratio for death was 0.68 (95% CI, 0.52-0.88) [24]. One major criticism of the study design is that brain imaging was not part of the standard staging or follow-up procedures unless neurologic symptoms were present. Given the high incidence of clinically undetected brain metastases, presumably some magnitude of benefit seen in this study could be attributable to treatment of patients with clinically undetected brain metastases.

Another more recent Japanese phase III randomized study evaluating the role of PCI in patients with ED-SCLC did enroll patients to determine whether PCI (25 Gy in 10 fractions) could affect survival [25]. In this study, brain MRI was required prior to initiation of PCI, and all patients who did not receive PCI underwent brain MRI every 3 months while enrolled on the study. The study reported a non-significant trend toward longer survival in patients who did not receive PCI (15.1 months in the control group vs. 10.1 months in the PCI group; P=0.09). On the basis of an interim analysis with these findings, the study was terminated for futility. Because patients in this study will undergo repeat staging with MRI brain prior to study enrollment after EP chemotherapy, we will not allow PCI.

Finally, recent studies suggest that anti-PD-1 therapy may penetrate the blood brain barrier to treat brain metastases in patients with NSCLC[26]. Among 11 NSCLC patients with untreated brain metastases, the brain metastasis response rate was 45% in the absence of any radiation therapy or surgical intervention. The duration of response was at least 12 weeks for 4 of 5 responders. This data suggests that treatment with immune checkpoint therapy as part of our clinical protocol may help to further reduce the incidence of clinically relevant brain metastases in patients with ED-SCLC.

### 1.1.6 Rationale for Nivolumab/Ipilimumab with Thoracic Radiation Therapy

The excellent response rates and OS rates with combined immune checkpoint blockade in the second line treatment of ED-SCLC outlined in Section 1.1.3 demonstrates that the immune system is actively involved in

SCLC tumor pathology. However, these responses are somewhat limited to patients that have preexisting T cells primed to target the tumor. Radiation therapy (RT) by itself has demonstrated clinical efficacy in multiple malignancies, including SCLC, by improving tumor control with limited toxicity and evolving evidence suggests RT may be a promising modality to combine with immunotherapy to amplify the immune response [27].

Cancer cells treated with noxious stimuli (*e.g.* chemotherapy or RT) undergo various forms of cell death, which results in differential antigenic presentation and clearance by the host [28]. Accumulating evidence indicates that RT can trigger an additional type of cellular demise termed immunogenic cell death (ICD) [29]. ICD is characterized by cell surface presentation and release of cryptic antigens, which have been termed danger-associated molecular patterns (DAMPs), into the surrounding tumor microenvironment [30]. RT-induced DAMP exposure has been demonstrated in various models *in vitro* and *in vivo* and is emerging as a therapeutic approach to increase the immune response. Prior studies have demonstrated that cancer cells that were treated with RT were able to prime a durable immune response to phenotypically similar cells when challenged in the opposite flank of a mouse [31]; this effect was found to be dependent on induced DAMP exposure. RT has also been found to increase MHC I expression [32], increase ligands that promote immune activity and enhance the profile of inflammatory soluble mediators in the tumor microenvironment [33]. Thus, it is hypothesized that RT is inducing an *in situ* vaccine of the targeted tumor and is aiding in overcoming the immunosuppressive environment.

In addition to the tumor targeted with RT, a burgeoning amount of evidence indicates tumors outside of the radiation field are also affected by the generation of this locally produced *in situ* vaccine. This phenomenon, though rare, is termed the abscopal effect and is thought to be mediated by the immune system [34]. This was first demonstrated in irradiated lung cancer cells which were inoculated into the footpads of mice followed by treatment with a dendritic cell (DC) growth factor; this study identified that the combination of immune stimulation and RT led to regression of pulmonary metastases, which were outside the irradiated field, and this was dependent on an intact immune system [35]. These findings were confirmed in other model systems [36, 37] and subsequent studies demonstrated that RT also increases T cell expansion, DC activation and cytokine release [38].

Though RT alone changes the antigen repertoire of the treated tumor and influences the distribution of immune effector cells, clinically this is not sufficient to maintain robust local responses and is unable to induce the abscopal effect in the majority of scenarios. Therefore, investigators have begun to combine RT with immune checkpoint blockade to create synergism between two highly effective tumor controlling modalities. This was first examined by combining RT with CTLA-4 blockade in a breast cancer model, which demonstrated that combination treatment compared to either alone resulted in improved local and distant control of the tumor burden [39]. Also, PD-1 deficient mice or PD-1 blockade lead to an abscopal effect in melanoma and renal cell cancer models [40]. Importantly, these preclinical findings have demonstrated merit in clinical studies. The abscopal effect has been recognized in combination with CTLA-4 blockade in melanoma [41] and NSCLC [42]. A recent retrospective study of melanoma patients also identified that RT + ipilimumab resulted in almost a doubling of OS and abscopal events were present in about 20% of patients [43]. The results of these clinical findings are encouraging and improved outcomes are likely as a more thorough understanding of the relationship between RT and immunotherapy evolves.

The organ(s) at risk in the treatment region must also be taken into consideration when combining RT with immunotherapy. In the setting of consolidative thoracic radiation therapy for SCLC, the most critical structure is the normal surrounding lung. This is important as both RT and immunotherapy separately have been shown to cause pneumonitis. Preclinical data of partial volume lung RT in rats revealed cytokine and immune cell responses were initiated at 1 hr following treatment and cyclic patterns of these responses were sustained up to sixteen weeks [44]. How these inflammatory responses induced by RT in the lung influence toxicity with immunotherapy are not known, but clinical data suggests that RT combined with immunotherapy may not lower the tolerance of the lung too drastically.

A retrospective study evaluating 16 patients with NSCLC who were prospectively enrolled in a phase 2 trial with phased ipilimumab and chemotherapy identified that adjuvant RT did not lead to any grade ≥ 3 toxicity [45]. Additionally, NSCLC patients that received RT followed by nivolumab [46] or a single patient in a case report who received concurrent RT and ipilimumab [42] did not have increased lung toxicity. Finally, a recent retrospective report of melanoma patients also indicated that patients that received RT before, during or after ipilimumab had no increased toxicity in the lung [43]. Combining RT, which can instigate a robust immune response, with checkpoint inhibition may provide synergism in immune-mediated destruction of SCLC tumors. By treating intrathoracic disease with consolidative RT after standard of care chemotherapy, the targeted tumor burden will be low and this may be the optimal time to amplify synergism between RT and immunotherapy.

### 1.1.7 Rationale to Support Nivolumab Monotherapy "Flat" Dose of 480 mg Every 4 Weeks

Nivolumab monotherapy has been extensively studied in NSCLC patient populations and in other solid tumor indications with body weight-normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of participants in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected in these studies, together with PK data from several phase I, II, and III clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients. It should be noted that a dose of 480 mg nivolumab across typical body weights leads to peak nivolumab concentrations that are less than 10mg/kg which has been previously shown to be safe and well tolerated across multiple clinical studies. Based on clinical modeling and simulation approaches using population PK (PPK) and exposure analyses of data from studies in multiple tumor types, a dose of 480mg delivered every 4 weeks is expected to be similarly efficacious compared to previously utilized dose strategies including 3mg/kg delivered every 2 weeks or 240mg flat dose delivered every 2 weeks. Nivolumab monotherapy has been extensively studied in multiple tumor types with body weight normalized dosing (mg/kg). Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients including increased flexibility between clinical visits,

as compared to a 2 week dosing schedule. A flat dose of 480 mg every 4 weeks was selected based on equivalence to the approved 3 mg/kg every 2 weeks at the median body weight of ~ 80 kg in nivolumab-treated subjects. A PPK model predicted overall nivolumab average exposures across subjects with a wide range of body weight from 480 mg Q4W to be similar to that from 3 mg/kg Q2W. Although the flat dose is expected to lead to higher exposure in lighter patients relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures are maintained below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerated dose across multiple tumor types. There was no clinically meaningful relationship between nivolumab exposure or body weight and frequency or severity of adverse events. Therefore, a flat dose of 480 mg every 4 weeks is expected to be safe and tolerable in patients. In terms of efficacy, 480 mg every 4 weeks is expected to result in similar efficacy given a flat exposure-response relationship and same dose intensity. Overall, the benefit-risk profile of nivolumab 480 mg Q4W is expected to be similar to the approved regimen 3 mg/kg Q2W, and it is recommended for further investigation in this study. Additionally, this simplified dose strategy will limit the number of visits and overall treatment administration inconvenience.

Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 480 mg nivolumab every 4 weeks will be similar to that of 3 mg/kg nivolumab every 2 weeks. Based on these clinical results, a flat dose of 480 mg every 4 weeks will be utilized for the maintenance dosing following completion of nivolumab/ipilimumab combination.

### 1.1.8 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some patients treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in a phase I study of nivolumab [47] and also in combination with ipilimumab [48]. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity.

With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore participants will be allowed to continue study therapy after initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST 1.1)-defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Such participants must discontinue study therapy upon evidence of further progression.

## 1.2 Background

### 1.2.1 Nivolumab Mechanisms of Action

Nivolumab is a fully humanized, IgG4 (kappa) isotype monoclonal antibody (mAb) that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. PD-

1, (CD279), a 55-kDa type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T cell activation on binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD 1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus. The emergence of these autoimmune phenotypes is dependent on the genetic background of the mouse strain, and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent on various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by mAbs can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (i.e., expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells *in vitro*. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells. Additional details are available in the Nivolumab Investigator Brochure.

### 1.2.2 Ipilimumab Mechanisms of Action

Ipilimumab is a fully humanized, IgG1 (kappa) isotype mAb that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of TILs. Inhibition of CTLA-4 signaling can also reduce Treg cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

### 1.2.3 Product Development Background

Nivolumab is in clinical development for the treatment of patients with NSCLC, RCC, glioblastoma, and other cancer types. Recently, nivolumab was approved by the FDA for the treatment of patients with advanced

NSCLC and melanoma. Nivolumab is also approved for the treatment of advanced melanoma in Europe, Japan, and other countries.

In the phase I/II trial (CA209-032), in participants with heavily pretreated SCLC, nivolumab monotherapy showed an ORR of 10%, whereas the combination of nivolumab-1 and ipilimumab-3 demonstrated an ORR of 30% [23]. Study CA209-451 is the second phase III study in the clinical development program for nivolumab in SCLC and will evaluate the efficacy and safety of nivolumab monotherapy and nivolumab and ipilimumab combination therapy, as maintenance treatment following first line platinum-based chemotherapy in patients with ED-SCLC.

## 1.3 Research Hypothesis

For patients with ED-SCLC and at least stable disease after 4 to 6 cycles of platinum-based chemotherapy, we hypothesize that ipilimumab and nivolumab with thoracic radiation therapy (30 Gy in 10 fractions) will improve 6-month PFS by at least 20% compared with a 6-month historical PFS rate of 24% among patients treated in a similar fashion without combined checkpoint blockade [5].

## 1.4 Overall Risk/Benefit Assessment

ED-SCLC is a disease with high unmet medical need. Despite robust initial response rates to first-line platinum-containing chemotherapy regimens, subsequent progression is typically rapid and overall survival rates are poor. Furthermore, there are currently no systemic agents approved in the maintenance setting for patients who respond to first-line therapy. The clinical activity of nivolumab and ipilimumab combination therapy, observed in the CA209-032 study, suggests the potential for improved clinical outcomes relative to a current standard practice of consolidative thoracic radiation therapy without nivolumab and ipilimumab combination therapy. Furthermore, thoracic radiation therapy delivered in close proximity to the nivolumab and ipilimumab combination therapy may lead to improved systemic anti-tumor response with the use of combined checkpoint blockade.

Nivolumab in combination with ipilimumab can cause clinically relevant AEs, including liver toxicities, thyroiditis, pneumonitis, and diarrhea. Most concerning when delivering the combination in conjunction with thoracic radiation therapy is the risk of clinically significant pneumonitis. We plan to carefully evaluate safety and tolerability of the proposed study regimen with a 6-9 patient safety lead in phase and a 13-week safety observation period prior to proceeding with our phase II study. Furthermore, completion of this single-arm phase II study will not only provide robust efficacy estimates but also robust safety data to help guide the design of future phase III randomized controlled trials for first-line treatment of patients with ED-SCLC.

# 2 OBJECTIVES

## 2.1 Primary Objective

### 2.1.1 Part 1: Safety Run In Phase I

The safety run in phase I is to confirm the recommended phase II dose of ipilimumab and nivolumab among patients treated with combined thoracic radiation therapy (30 Gy in 10 fractions) and nivolumab/ipilimumab following standard treatment with 4-6 cycles of platinum-based chemotherapy.

### 2.1.2 Part 2: Phase II

Phase II objective is to estimate the 6-month PFS rate among patients treated with ipilimumab and nivolumab with thoracic radiation therapy (30 Gy in 10 fractions) after standard treatment with 4 to 6 cycles of platinum-based chemotherapy.

## 2.2 Secondary Objectives

1. To estimate the median PFS among patients treated with ipilimumab and nivolumab with thoracic radiotherapy (30 Gy in 10 fractions) after standard treatment with 4-6 cycles of platinum-based chemotherapy.

2. To estimate 1-year OS rate among patients treated with ipilimumab and nivolumab with thoracic radiotherapy after standard treatment with 4-6 cycles of platinum-based chemotherapy.

3. To estimate median OS among patients treated with ipilimumab and nivolumab with thoracic radiotherapy after standard treatment with 4-6 cycles of platinum-based chemotherapy.

## 2.3 Exploratory Objectives

1. To document and explore patterns of radiographic response and progression both inside and outside the treated radiotherapy field.

2. To bank and store formalin-fixed, paraffin-embedded diagnostic tumor biopsy specimens for future potential predictive and/or prognostic biomarkers.

3. To bank and store peripheral blood specimens for future rigorous evaluation of future potential predictive and/or prognostic biomarkers.

# 3 ETHICAL CONSIDERATIONS

## 3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements. The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to Moffitt Cancer Center through the MCRN Coordinating Center immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

## 3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to participants and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## 3.3 Informed Consent

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given to participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the patient volunteers to participate. The main site study team will provide the investigator with an appropriate sample informed consent form, which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2. Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.

3. Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.

4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information.

5. If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

6. Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF and, in the US, the participant's signed HIPAA Authorization.

The consent form must also include a statement that the study sponsor, Moffitt Cancer Center, BMS and regulatory authorities have direct access to patient records. Participants unable to give their written consent (e.g., stroke or participants with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

# 4 INVESTIGATIONAL PLAN

The principal investigator is ultimately responsible for appropriate study coordination.

## 4.1 Safety Lead in Design

All patients for the entire study will be treated on the same schedule outlined in Section 4.2. We will utilize a 6 to 9 patient safety lead in endpoint as described in the Section 9.1 with a safety observation period of 13 weeks after initiation of thoracic radiation therapy. We will initially enroll 6 patients and wait until completion of the 13-week safety observation period following initiation of ipilimumab + nivolumab combination treatment. No additional patients will be enrolled until the safety lead in phase is complete.

If 0 or 1 of 6 patients develops unacceptable toxicity:

then we will proceed with the study as outlined below (to accrue an additional 44 patients).

If 2 patients develop unacceptable toxicity:

then we will enroll an additional 3 patients to determine the rate of unacceptable toxicity with 9 patients.

If 3 or more patients develop unacceptable toxicity during any portion of the safety lead in phase,

then we will discontinue the study.

Additionally, we will be continually assessing toxicity throughout the study and if at any time 3 of the first 9 patients or greater than 33% of patients experience unacceptable toxicity within the 13-week safety observation period, we will discontinue the study. After the 13-week safety observation period, toxicity will be assessed on an ongoing basis for all patients prior to each dose of ipilimumab/nivolumab or nivolumab alone until study completion. If unacceptable toxicity occurs outside the 13 week safety observation period, that patient will discontinue treatment on the study according to discontinuation criteria (Section 6.5.3.4). The protocol monitoring committee will evaluate all patients who discontinue the study due to unacceptable toxicity on a monthly basis. If the monitoring committee feels that the study regimen is unsafe, we will discontinue the study.

## 4.2 Phase I/II Study Design and Duration

This is a non-randomized, single-arm, multicenter, phase I/II study in adult patients with ED-SCLC, who achieved stable disease, partial response, or complete response after completion of platinum-based first-line chemotherapy. Fifty participants will be enrolled to receive thoracic radiation therapy (30 Gy in 10 fractions) followed by nivolumab/ipilimumab combination therapy for 4 cycles and then maintenance nivolumab until progression. The study design schematic is presented in Figure 4.2-1.

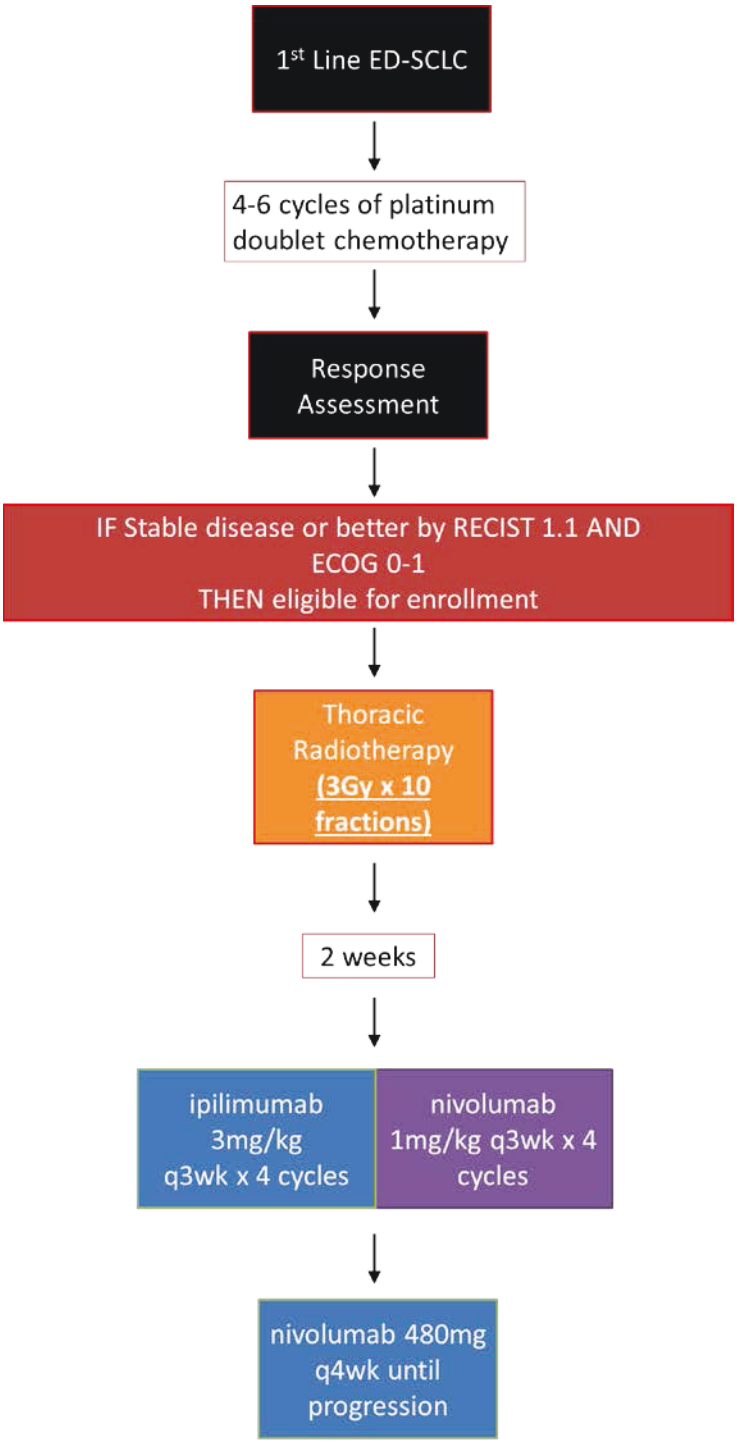


**Figure 4.2-1.** Study Schematic

The treatment regimen is as follows:

At least 3 weeks, but not longer than 8 weeks after completion of systemic chemotherapy, patients will initiate thoracic radiation therapy targeting the initially involved supraclavicular, hilar and mediastinal lymph node stations as well any other residual intrathoracic disease seen on restaging CT or PET-CT after completion of systemic therapy. Details of the Radiotherapy Treatment Schedule are outlined in Table 5.2-1. At least 14 days and not more than 21 days after completion of RT, patients will commence nivolumab 1 mg/kg (30-minute IV infusion) and ipilimumab 3 mg/kg (90-minute IV infusion) every 3 weeks for 4 doses, followed by nivolumab 480 mg every 4 weeks, as described in Table 6.5-1.

The detailed 3-part schedule of investigational treatments is as follows:

**1)** Monday to Friday: thoracic radiation therapy at a dose of 3 Gy daily for 10 treatments

**2)** After at least 14 days but not more than 21 days, initiate combined nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses;

**3)** After part 2 of treatment, initiate maintenance nivolumab at least 42 days but not more than 56 days, delivered every 4 weeks at a dose of 480 mg/cycle.

Patients will undergo ongoing 4-week cycles until discontinuation criteria are met (Section 4.6). The full study schedule calendar is outlined in Appendix 1.

On-study tumor assessments commence 4 weeks after initiation of thoracic radiation therapy and will be conducted according to the study calendar schedule(+/-5 days) for the first 33 weeks. After week 36, radiographic tumor assessments will be performed every 12 weeks (+/-5 days) until disease progression (See Tables 7.4-1 and 7.4-2).

The total duration of the study from start to final analysis of overall survival is expected to be 30 months (18 months of accrual + 12 months of follow-up), assuming an increasing accrual rate from 2 participants/month for the first 6 months, then increasing accrual rate (5 participants/month during 18 months). PFS will be analyzed before OS (Section 9). Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded. Participant safety will be monitored on an ongoing basis as described fully in Section 7.

The start of the trial is defined as first visit for the first participant screened. The end of trial is defined as the last visit for the last participant. Study completion is defined as the final date on which data for the primary endpoint was collected.

### 4.2.1 Study Phases

The study is divided into the following phases: Screening, Treatment, and Follow-up.

The study calendar is outlined in Appendix 1.

**1. Screening:** Screening begins after the participant signs the informed consent form (ICF) and is enrolled on the study through the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center**.**

- Whenever possible, tumor tissue (archival or recent tumor biopsy 10 slides or tissue block) should be submitted to the central lab for correlative studies. Participants must consent to allow the acquisition of tumor tissue by study personnel for performance of the correlative studies.

- Baseline assessments must be performed within the timeframes described in Table 7.1-1.

- For patients with known brain metastases at presentation, brain radiotherapy (whole brain radiation therapy (WBRT) or stereotactic radiation) may be offered, per local standard of care. Patients with asymptomatic brain metastases at initial diagnosis may be treated with chemotherapy alone at the discretion of the patient's treating physician. A 4 week disease stable interval as confirmed by MRI or CT brain w/ contrast (Table 7.4-2) is required after treatment of brain metastases before initiation of thoracic radiation therapy.

- Prophylactic Cranial Irradiation (PCI) is not allowed.

- Treatment initiation must be > 3 weeks but ≤ 8 weeks from the last dose of chemotherapy for all participants.

- The screening phase either ends with confirmation of full eligibility and initiation of study treatment or with the confirmation that the participant is a screen failure.

- This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure before enrollment If re-enrolled, the participant must be reconsented. A new participant identification number will be assigned at the time of re-enrollment.

**2. Treatment:** The treatment phase begins with a study initiation call to the MCRN. Treatment is to begin within 3 business days of study initiation.

Study therapy is administered as described in Tables 5.2-1 and 6.5-1 until disease progression, discontinuation due to toxicity, withdrawal of consent, the study ends, or other criteria for discontinuation are met, as described in Section 4.6 and Section 6.5.3.4. Patients may be treated beyond initial progression as specified in Section 6.5.5.

Participants will be evaluated for response according to RECIST 1.1 criteria. Radiographic assessments will be obtained according to the study calendar schedule for the first 33 weeks and subsequently every 12 weeks, or more frequently as clinically indicated, until disease progression (or until discontinuation of study drug(s) in patients treated beyond progression) or withdrawal of study consent.

The treatment phase ends when the participant is discontinued from study drug(s)

Study assessments while on treatment are to be collected as outlined in Tables 7.1-1, 7.1-2, and 7.1-3.

**3. Follow-up.** Follow-up begins when the decision to discontinue a participant from study therapy is made.

Participants who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments according to the study calendar(± 5 days)for the first 33 weeks, and subsequently every 12 weeks, until disease progression or withdrawal of study consent.

Follow-up visits occur as follows:

– X01 Follow-up Visit 1 = 35 days ± 7 days from last dose;

– X02 Follow-up Visit 2 = 80 days ± 7 days from X01 Follow-up Visit 1;

– Survival Follow-Up visits begin after the X02 Follow-up Visit 2.

For Survival Follow-up Visits, contact of participants will occur (in person or by telephone) every 12 weeks upon entry into this phase to evaluate OS and collect data on the initiation of subsequent therapy for the treatment of SCLC.

## 4.3 Post-Study Access to Therapy

At the conclusion of the study, participants assigned to active study drug who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study drug if any of the following occur: 1) the marketing application is rejected by responsible health authority; 2) the study is terminated due to safety concerns; 3) the participant can obtain medication from a government-sponsored or private health program; or 4) therapeutic alternatives become available in the local market.

## 4.4 Study Population

For entry into the study, the following criteria MUST be met.

### 4.4.1 Inclusion Criteria

*1. Signed Written Informed Consent*

a) Participants must have signed and dated an IRB/IEC-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

*2. Target Population*

a) Patients with SCLC documented by histology or cytology from brushing, washing, or needle aspiration of a defined lesion, but not from sputum cytology alone;

b) Participants must have presented at initial diagnosis with extensive-stage disease (defined as Stage IV (T any, N any, M1a/b) per NCCN Guidelines Version 1.2015, AJCC Cancer Staging Manual, 7th Edition, 2010);

c) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 (see http://ecog-acrin.org/resources/ecog-performance-status for details)

d) Participants must have received 4-6 cycles of platinum-based first-line chemotherapy and must have an ongoing response of complete response (CR), partial response (PR), or stable disease (SD) after completion of chemotherapy. Acceptable combinations, as recommended per NCCN guidelines, include cisplatin or carboplatin combined with either etoposide or irinotecan;

i) As an exception to the above criterion, participants receiving only 3 cycles of chemotherapy due to toxicity are eligible, if they have an ongoing PR or CR after the 3rd cycle

ii) Participants who have received > 6 cycles of platinum-based first-line chemotherapy are not eligible

e) Participants must initiate study treatment with thoracic radiation therapy ≤ 8 weeks (56 days) from the last dose of platinum-based first line chemotherapy;

i) Thoracic radiation therapy must not be administered < 3 weeks (21 days) from the last dose of platinum-based first line chemotherapy

ii) Ipilimumab/nivolumab study therapy must not be administered < 13 days and not more than 21 days from the last dose of thoracic radiotherapy

f) Whenever possible, a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation should be made available and submitted to the central lab for correlative studies;

g) Patient re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study due to pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented.

*3. Age and Reproductive Status*

a) Men and women ≥ 18 years of age;

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of thoracic radiation therapy;

c) Women must not be breastfeeding;

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion;

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of the study drug (half-life up to 25 days) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion;

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

Regarding male participants, age 18 years or greater:

a) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) study therapy plus 5 half-lives of the study drug study therapy up to 25 days plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion;

b) Azoospermic males are exempt from contraceptive requirements;

c) Male participants must be willing to refrain from sperm donation during the entire study and for 5 half-lives of study drug plus 90 days (duration of sperm turnover).

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

At a minimum, participants must agree to the use of one highly effective method of contraception as listed below:

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP participants and female partners of male participants who are WOCBP are expected to use one of the highly effective methods of contraception listed below. Male participants must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

- Progestogen-only hormonal contraception associated with inhibition of ovulation.

- Hormonal methods of contraception, including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena®

- Nonhormonal IUDs, such as ParaGard®

- Bilateral tubal occlusion

- Vasectomized partner with documented azoospermia 90 days after procedure

    - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

- Intrauterine hormone-releasing system (IUS)

- Complete abstinence

    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse

    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days);

    - It is not necessary to use any other method of contraception when complete abstinence is elected;

    - Participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 7.

    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the participant chooses to forego complete abstinence.

    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)

2) Withdrawal (coitus interruptus)

3) Spermicide only

4) Lactation amenorrhea method (LAM)

## 4.4.2 Exclusion Criteria

*1. Target Disease Exceptions*

a) Participants with previous brain metastases are eligible provided that they are treated and asymptomatic not requiring steroids or anticonvulsants, and have stable disease at the screening tumor assessment. A 4 week disease stable interval as confirmed by MRI or CT brain w/ contrast (Table 7.4-2) is required after treatment of brain metastases before initiation of thoracic radiation therapy. In addition, subjects must have been either off corticosteroids, or on a stable or decreasing dose of □□10 mg daily prednisone (or equivalent).

b) Participants who have received prior chest radiation which at the discretion of the treating radiation oncologist precludes delivery of protocol radiation therapy as outlined in section 5 .

c) Carcinomatous meningitis

d) Pleural effusion that cannot be controlled with appropriate interventions

e) All toxicities attributed to prior anti-cancer therapy must have been resolved to Grade 1 (NCI CTCAE Version 4) or baseline before administration of study drug(s) other than:

> i) Patients with toxicities attributed to prior anti-cancer therapy that either are not expected to resolve and/or result in long-lasting sequelae, such as neuropathy after platinum-based therapy, or are not expected to interfere with treatment on study, such as fatigue,alopecia, or grade 2 hematologic toxicityare eligible.

*2. Medical History and Concurrent Diseases*

a) Women who are pregnant or breastfeeding

b) Active, known, or suspected autoimmune disease. Patients with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment are excluded. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

c) A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study initiation. Corticosteroids with minimal systemic absorption (inhaled or topical steroids) and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease

d) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways)

e) Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

f) Any patient requiring supplemental oxygen therapy

g) Previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period

h) Known medical condition that, in the investigator’s opinion, would increase the risk associated with study participation or study drug(s) administration or interfere with the interpretation of safety results

i) Major surgery or significant traumatic injury that is not recovered at least 14 days before the initiation of thoracic radiation therapy.

*3. Physical and Laboratory Test Findings*

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBVsAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection

i) Individuals with a positive test for HCV antibody but no detection of HCV RNA indicating no current infection are eligible

b) Known medical history of testing positive for human immunodeficiency virus (HIV) or known medical history of acquired immunodeficiency syndrome (AIDS)

c) Inadequate hematologic function defined by:

i) Absolute neutrophil count (ANC) < 1,000/$mm^3$.

ii) Platelet count < 100,000/$mm^3$, or

iii) Hemoglobin level < 8.0 g/dL

d) Inadequate hepatic function as defined by either:

i) Total bilirubin level ≥ 1.5 times the ULN (except patients with Gilbert Syndrome, who are excluded if total bilirubin ≥ 3 times ULN), or

ii) AST and ALT levels ≥ 2.5 times the ULN or ≥ 5 times the ULN if liver metastases are present

e) Inadequate pancreatic function as defined by either:

i) Lipase > 1.5 ULN. Participants with lipase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

ii) Amylase > 1.5 ULN. Participants with amylase > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

*4. Allergies and Adverse Drug Reaction*

a) History of allergy or hypersensitivity to any of the study drugs or study drug components

*5. Other Exclusion Criteria*

a) Prisoners or individuals who are involuntarily incarcerated

b) Individuals who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

### 4.4.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Postmenopausal women may continue HRT after FSH testing is completed and postmenopausal status is confirmed. Other parenteral products may require washout periods as long as 6 months.

## 4.5 Concomitant Treatments

### 4.5.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE or an autoimmune paraneoplastic syndrome). Participants with an autoimmune paraneoplastic syndrome at enrollment requiring concurrent immunosuppressive treatment are not eligible;
- Systemic corticosteroids > 10 mg daily prednisone equivalent, except as stated in Section 4.4.2 or to treat a drug-related AE;
- Any concurrent systemic antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for the treatment of cancer);
- Supplemental oxygen therapy
- Surgical resection of tumor;

• Note: in addition to the study prescribed thoracic radiotherapy, the following radiotherapy is permitted:

– Palliative bone radiotherapy as described in Section 4.5.2

– Palliative radiotherapy to a single metastatic site, other than bone, in participants who do not require immediate initiation of second-line systemic anti-cancer therapy. See Section 4.5.2 for additional restrictions.

## 4.5.2 Other Restrictions and Precautions

Treatment breaks must be resumed ≤ 6 weeks from the last dose or the participant must be permanently discontinued from the study. (See exceptions in Sections 4.6 and 6.5.3)

Non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy at any time while on study treatment. Radiotherapy to non-bone lesions is permitted only as described in Section 4.5.2, but must not be given during or 2 weeks after study therapy. Details of palliative radiotherapy should be documented in the source records and case report form (CRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

Participants requiring palliative radiotherapy should be carefully assessed for disease progression. Participants considered to have progressive disease are required to discontinue study participation, unless eligible to continue treatment beyond progression per the guidance in Section 6.5.5 (Treatment Beyond Disease Progression).

***Imaging Restrictions and Precautions***

It is the local imaging facility's responsibility to determine, based on patient attributes (e.g., allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether they should receive contrast and, if so, what type and dose of contrast is appropriate. Specific to MRI, patients with severe renal insufficiency (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m$^2$) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

## 4.5.3 Permitted Therapy

Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses including doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact

allergen) is permitted. Postmenopausal women may continue HRT after FSH testing is completed and postmenopausal status is confirmed. Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) are allowed. See Section 4.5.2 for guidance on concomitant palliative radiotherapy. Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with study therapy. Discontinuation of the use of herbal medications prior to study initiationis encouraged.

## 4.6 Discontinuation of Participants Following Any Treatment with Thoracic Radiation Therapy or Study Drug(s)

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Disease progression as assessed by RECIST 1.1 criteria, unless the participant meets criteria for treatment beyond progression (Section 6.5.5)
- Participant requests to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Discontinuation of study support by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Additional protocol-specified reasons for discontinuation, as described in Section 6.5.3.4

In the case of pregnancy, the investigator must immediately notify the primary investigator or designee of this event. In most cases, study drug(s) will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the primary investigator or designee, the IRB, and the Sponsor or designee must occur. All participants who discontinue study drug(s) should comply with protocol specified follow-up procedures as outlined in Section 7. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Participants must be followed for at least 100 days after the last dose of study therapy. Follow-up visit 1 (FU1) occurs approximately 35 days (+/- 7 days) after last dose of coinciding with the date of discontinuation (+/- 7 days) if the date of discontinuation is greater than 35 days after the last dose. Follow-up visit 2 (FU2) occurs approximately 80 days (+/- 7 days) after FU1. Survival visits are every 3 months from FU2 up to 5 years and may be conducted during a clinic visit or via the phone. The primary endpoint of this study is PFS with a secondary endpoint of OS so tracking reporting the participant's status in the follow-up setting according to the protocol guidelines for disease progression and survival are critical to the final study analysis. The importance of follow-up should be clearly communicated to study participants. If the study drug(s) is discontinued prior to

the patient completion of the study, the reason for the discontinuation must be documented in the patient's medical records and entered on the appropriate case report form (CRF) page.

## 4.7 Post-Study Drug Study Follow-up

In this study, overall survival is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 7 until death or the conclusion of the study. The primary investigator may request that survival data be collected on all participants outside of the protocol-defined window (see Table 7.1-5). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

### 4.7.1 Withdrawal of Consent

Participants who request to discontinue study therapy will remain on the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up in writing, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study therapy only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### 4.7.2 Lost to Follow-Up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with those authorized by the particpant as noted above. Lost to follow-up is defined as the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information. If after all attempts the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

# 5 RADIATION THERAPY

## 5.1 Thoracic Radiation Dose Specifications

Patients will receive thoracic radiation to residual intrathoracic disease including mediastinal, supraclavicular (SC), and hilar lymph node sites involved at the time of diagnosis. The treating physician will have discretion to limit treatment volume if there is concern for excess of normal tissue irradiation.

The total dose of 30 Gy will be given in 10 daily fractions of 3 Gy prescribed to the planning target volume (PTV) with at least 95% of the PTV receiving 30 Gy. An acceptable variation is at least 90% of the PTV receiving 30 Gy. The maximum dose for any contiguous volume of no more than 0.03 cc inside the PTV must not exceed 120% of the prescribed dose. An acceptable deviation is a maximum dose inside the PTV of up to 125% of the prescribed dose. The minimum dose (0.03 cc) to the PTV volume should be no less than 28.5 Gy. An acceptable deviation is a minimum PTV dose of 27.9 Gy. All radiation doses will be calculated with inhomogeneity corrections.

## 5.2 Radiation Treatment Schedule

Localization, Simulation, and Immobilization for radiation treatment planning, as outlined in Section 5.4, will be performed no more 21 days and no less than 1 day before the first day of thoracic radiation treatment. The patient can initiate treatment any day of the week. Treatment will be delivered daily for 10 consecutive working days (generally Monday-Friday). Disruptions to the planned radiation treatment schedule should be avoided if at all possible. Any unexpected treatment break lasting > 1 day should be reported to the principal investigator.

**Table 5.2-1.** Radiation Treatment Schedule

| Thoracic RT Planning Simulation | Radiation Treatment 1-5 | Radiation Treatment 6-10 |
|---|---|---|
| Between Day -21 and Day 0 | Week 1 | Week 2[A] |

[A]If thoracic radiation therapy is started later in week 1, then radiation treatments will continue into week 3.

## 5.3 Technical Factors

### 5.3.1 Beam Energy

Six- to 10-MV photons are recommended for mediastinal and lung irradiation; however, beam energy and type will be left to the discretion of the treating radiation oncologist in order to obtain the best dose distribution for the site being treated.

### 5.3.2 Beam Shaping

Multi-leaf collimation (MLC) or individually shaped custom blocks should be used to protect normal tissues outside of the target volume.

## 5.4 Localization, Simulation, and Immobilization

A volumetric treatment planning computed tomography (CT) study (intravenous contrast preferred, if possible) will be required for treatment of primary disease and regional lymphatics. A four-dimensional CT to account for respiratory motion may be beneficial and should be utilized whenever possible to limit the overall size of the planning target volume. PET-CT performed for restaging may also assist with radiation treatment planning target delineation. Evaluation and/or fusion (according to each institution's standard practice) of the initial diagnostic PET-CT or CT chest will assist with delineation of any initially involved hilar or mediastinal nodal sites.

Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices with a no more than 3-mm thickness will be obtained through the regions harboring gross disease and the entirety of all organs in the treatment field. This is necessary for proper radiation planning.

## 5.5 Treatment Planning/Target Volumes

The definitions of volumes will be in accordance with the 1993 ICRU Reports #62.

*Definition of GTV*: Gross tumor volume (GTV) will include known disease as determined by physical examination and post-chemotherapy imaging studies. The Uniform Tissue Naming scheme for this study is available in Table 5.6-2.

*Definition of CTV*: The clinical target volume (CTV) will be defined as any residual intrathoracic disease contoured as GTV plus 0-1cm (preferable 0.7cm) expansion volume accounting for anatomic boundaries. Additionally, the CTV volume will include any SC, hilar or mediastinal lymph node sites that were involved at the time of initial diagnosis. This is not the same as pretreatment volume. For example, if the patient had a 10 cm mediastinal mass that involved the paratracheal and subcarinal lymph nodes and had a complete response to chemotherapy, the CTV would not necessarily be a 10 cm volume but rather a carefully defined volume including the subcarinal and paratracheal tissues. CTVs will be labeled to correspond to the appropriate GTV or in cases where there is no GTV, the CTV will be labeled according to Uniform Tissue Naming scheme in Table

5.6-2.CTV may be modified to exclude intrathoraic pulmonary nodules as well as nodal regions if they contribute to excess normal tissue toxicity.

*Definition of PTV*: The planning target volume (PTV) is the CTV plus a margin to account for treatment set-up uncertainty and organ motion. The most appropriate PTV margin is to be determined by the treating radiation oncologist and could range from 0.3 to 2.0 cm depending on the use of respiratory motion management and image guided radiation therapy techniques.

Utilization of advanced planning techniques including 3D conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) to minimize dose to normal tissues (especially lung) is encouraged.

*Respiratory Motion Assessment and Management:*

Utilization of advanced planning techniques to account for respiratory motion can limit the volume of normal tissue (specifically lung). By utilizing respiratory motion management, the PTV margin that accounts for organ motion can be made smaller. 4D-CT based planning to account for any residual tumor motion as well as hilar-mediastinal motion is one form of respiratory motion management. Alternative options to account for respiratory motion include but are not limited to fiducial marker placement, gating and breath hold approaches.

*Internal Target Volume (ITV) Approach:*

If a 4D-CT was collected at the time of simulation for respiratory motion management, then an ITV approach can be utilized to account for internal motion. Utilization of an ITV approach allows for limiting PTV expansion as outlined above. ITV approach can be utilized to account for motion of any residual intrathoracic tumor through designation of GITV or it can be utilized to delineate CTV motion at the hilar or mediastinal sites through designation of a CITV.

*3DCRT Treatment Planning:*

The PTVs are to be treated with any combination of coplanar or non-coplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to normal tissues. Field arrangements will be determined by the 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of volumetric dose, including DVH analysis of the cumulative dose to each PTV and all critical normal structures.

*IMRT Treatment Planning:*

IMRT is allowed at the discretion of the treating radiation oncologist. If IMRT is used, it is highly encouraged that a 4D-CT is also performed.

## 5.6 Target Volume and Critical Structure Constraints with Compliance Criteria

**Table 5.6-1.** Target Volume and Critical Structure Constraints with Compliance Criteria

| Structure | Dose Constraint | Acceptable Variation | Unacceptable Deviation |
|---|---|---|---|
| PTV | 30Gy >= 95% | 30Gy > =90% | 30Gy < 90% |
| | Min (0.03cc) > =28.5Gy | Min (0.03cc) > =27.9Gy | Min (0.03cc) < 27.9Gy |
| | Max (0.03cc) <= 36Gy | Max (0.03) <= 37.5Gy | Max (0.03) > 37.5Gy |
| Lungs | V20Gy <= 20% | V20Gy <= 35% | V20Gy > 35% |
| | Mean < =15Gy | Mean < =20Gy | MLD > 20Gy |
| Liver | > 700 cc <= 10 Gy | > 700 cc < =18 Gy | < 700 cc <= 18 Gy |
| Spinal cord | Max (0.03cc) < =36Gy | NA | Max (0.03cc) > 36Gy |
| Heart | Max (0.03cc) < =36Gy | Max (0.03cc) > 36Gy | NA |
| | V30Gy < =30% | V30Gy > 30% | Min (0.03) > 30Gy |
| Esophagus | Max (0.03cc) <= 36Gy | Max (0.03cc) > 36Gy | NA |

Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the DICOM standard name listed.

Table 5.6-2 outlines the naming of the various normal and critical structures for radiation treatment plan submission.

| **Table 5.6-2.** Uniform Tissue Naming Scheme and Descriptions | |
|---|---|
| **DICOM Standard Name** | **Description** |
| GTV | Gross Tumor Volume<br>Required for lesions that have not had CR to chemotherapy unless using GITV |
| GITV | Gross Internal Tumor Volume (*if using ITV approach)<br>Optional |
| CTV | Clinical Target Volume<br>Required - unless using CITV |
| CITV | Clinical Internal Target Volume (*if using ITV approach)<br>Optional |
| PTV | Planning Target Volume<br>Required |
| Lungs | Right Lung + Left Lung minus GTV<br>Required |
| Heart | Heart/Pericardium<br>Required |
| Esophagus | Esophagus<br>Required |
| Spinal Cord | Spinal Cord<br>Required |
| Non-PTV | External minus PTV<br>Required |
| Liver | Liver (*if in path of beam)<br>Optional |

## 5.7 Documentation Requirements

Portal images of each field must be obtained on or before the first day of therapy but will not be submitted.

If IMRT is used, portal images will not be obtained, but patient specific QA will be performed prior to the first fraction.

Verification films of each site will be done weekly, but not submitted.

Cone beam CT, kV imaging, or other in-room imaging for set-up is allowed.

Isodose plans for 3D radiotherapy or IMRT planning with DVHs of GTV, CTV, PTV, and critical structures are required.

Acceptable variations are allowed only when the geometrical arrangement of the target and critical structures is challenging. Unacceptable deviations should be avoided whenever possible and plan modifications should be attempted to improve results. Ultimately, the decision to deliver the proposed radiation treatment plan falls to the treating radiation oncologist. The details of each radiation treatment plan are to be collected by the study sponsor and all acceptable variations and unacceptable deviations will be appropriately documented in the study record.

## 5.8 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Principal Investigator, Bradford Perez, MD, or designee, will perform an RT Quality Assurance review for the first case from each study site prior to initiation of radiation therapy. At least 3 business days should be allowed for case review. Once the initial case from each institution has been carefully reviewed and deemed acceptable, all other patients will be treated according to the protocol guidelines by the treating radiation oncologist. All cases will be reviewed within 3 months after the study has reached the target accrual or as soon as complete data for all cases enrolled have been received at Moffitt Cancer Center.

## 5.9 Radiation Therapy Adverse Events

Side effects of treatment will vary depending on the location of disease and volume of normal tissues in or near the radiation planning target volume. All attempts should be made to minimize adverse effects by limiting the normal tissue radiation dose (especially to the lung) as much as possible and adhering to the normal tissue dose constraints of this study.

### 5.9.1 Acute Reactions

It is likely that all patients treated on study will develop some level of fatigue. Alopecia, skin hyperpigmentation, and erythema are possible acute side effects that are generally well tolerated. Cough and esophagitis (if the esophagus is within or near the planning target volume) are likely. Severe esophagitis requiring intravenous hydration, therapy interruption, or feeding tube, severe cough, shortness of breath, and hemoptysis are possible but less likely.

### 5.9.2 Late Reactions

Asymptomatic fibrotic changes in the lung seen on chest imaging are likely. Severe fibrosis of lung resulting in severe respiratory compromise, symptomatic esophageal stricture, radiation pericarditis, and myocardial injury, spinal cord injury, and brachioplexopathy are possible but unlikely adverse effects of radiation.

### 5.9.3 Treatment of Radiation Adverse Events

All attempts should be made to limit the symptoms and the overall impact of acute and late effects of radiation. Esophagitis should be treated empirically for candidiasis with fluconazole or nystatin, and managed with topical anesthetic, H2 blocker or proton pump inhibitor, NSAIDs, or narcotic pain medications, if necessary.

# 6 STUDY DRUGS

Study drugs include both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP), including the following (**Table 6-1**):

**Table 6-1.** Study Drugs for MCC 18914

| Product Description/Class and Dosage Form | IP/Non-IMP | Potency | Packaging/ Appearance | Storage Conditions (per label) |
|---|---|---|---|---|
| Nivolumab Solution for Injection | IP | 100 mg (10 mg/mL) | 10 mL/vial (5 or 10 vials/carton) | Store at 2-8°C; protect from light and freezing |
| Ipilimumab Solution for Injection | IP | 200 mg (5 mg/mL) | 40 mL/vial (4 vials/carton) | Store at 2-8°C; protect from light and freezing |

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent or placebo (ie, 0.9% sodium chloride injection or 5% dextrose injection) should also be sourced by investigative sites if available and permitted by local regulations.

## 6.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this protocol, the investigational medicinal products are:

- Nivolumab
- Ipilimumab

## 6.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products. Non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

## 6.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as outlined in the investigator's brochure. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact the principal investigator and BMS immediately. Study drug not supplied by BMS will be stored in accordance with the package insert. Please refer to Section 10.2.2 for guidance on IP records and documentation. Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations. Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab. The infusion duration of nivolumab is 30 minutes and for ipilimumab is 90 minutes.

## 6.4 Method of Assigning Participant Identification

Every participant that signs the informed consent form must be assigned a participant number. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by principle investigator.

All participants must be registered with the MCRN Coordinating Center to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Participants failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number, if indicated. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the participant of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient, the completed and signed eligibility checklist along with supporting documentation must be sent to the MCRN via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM (EST).

## 6.5 Selection and Timing of Dose for Each Participant

The dosing schedules are detailed in Table 6.5-1.

**Table 6.5-1.** Dosing Schedule (Cycles 1-3)

| **Cycles 1 and 2 (42-day [6 week] cycles)** | | **Cycle 3 (28-day [4 week] cycles)** |
|---|---|---|
| **Day 1** | **Day 22** | **Day 1** |
| 1 mg/kg Nivolumab (diluted to 100 mL) | 1 mg/kg Nivolumab (diluted to 100 mL) | 480 mg Nivolumab (48 mL diluted 100 mL) |
| 3 mg/kg Ipilimumab (diluted to 100 mL) | 3 mg/kg Ipilimumab (diluted to 100 mL) | |

For participants weighing < 35 kg, nivolumab and ipilimumab must be diluted to 50 mL in 0.9% sodium chloride or 5% dextrose solution.

All participants will be monitored continuously for adverse events (AEs) while on study treatment. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and AE criteria, as described in Sections 6.5.3.

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be the ipilimumab study drug and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Ipilimumab must be diluted to 100 mL in 0.9% sodium chloride solution or 5% dextrose solution. Nivolumab must be diluted to 100 mL 0.9% sodium chloride solution or 5% dextrose solution. For weight-based dosing, if the participants weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard. There will be no dose modifications allowed.

### 6.5.1 Dosing Windows

During Cycles 1 and 2:

- Participants may be dosed with ipilimumab 3 mg/kg and nivolumab 1 mg/kg with no less than 19 days between
  - C1D1 and C1D21
  - C1D21 and C2D1
  - C2D1 and C2D21
  - C2D21 and C3D1

During Cycle 3 and beyond:

- Participants may be dosed no less than 27 days from the previous dose of drug

Participants may be dosed up to 3 business days after the scheduled date if necessary, or longer in the event of a toxicity requiring dose delay. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

### 6.5.2 Study Medications

Nivolumab 1 mg/kg (30 min IV infusion) and ipilimumab 3 mg/kg (90 minute IV infusion) will be administered every 3 weeks for 4 doses, followed by nivolumab 480 mg every 4 weeks. The rationale for this dose schedule is provided in Section 1.1.7. The schedule of investigational treatments is divided into two 42-day cycles at the start of therapy, followed by ongoing 4-week cycles. This dosing schedule is described in detail in Table 6.5-1.

Refer to the Pharmacy Information sheets for more detail. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, participants should be managed according to Section 6.5.6. See Section 6.5.4 for information on Management Algorithms for Immuno-Oncology Agents.

### 6.5.3 Dose Modifications and Delays

#### 6.5.3.1 Dose Modifications

Dose reductions and discontinuation of ipilimumab or nivolumab for the management of toxicities of individual participants are permitted at the discretion of the treating physician Dose escalations are not permitted.

#### 6.5.3.2 Dose Delays

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both).

Study therapy administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:

– Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

- Any Grade 3 skin, drug-related adverse event

- Any Grade 3, drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:

– Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay

– If a participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity

– If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

- Any adverse event, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication

#### 6.5.3.3 Criteria to Resume Treatment

Participants may resume treatment with study therapy when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue

- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin

- Drug-related pulmonary toxicity must have resolved to baseline before treatment is resumed

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled timepoint per protocol. Doses should not be skipped.

If treatment is delayed > 6 weeks (42 days) from the last dose due to drug-related toxicity, the participant must be permanently discontinued from study therapy, except as specified in Section 6.5.3.4. In the event treatment is

delayed > 6 weeks due to reasons other than study drug-related toxicity, the case should be discussed with the Principal Investigator before proceeding.

#### 6.5.3.4 Discontinuation Criteria

Treatment with study therapy should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:

  – Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

  – Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

    ♦ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

    ♦ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

      o AST or ALT > 8 x ULN

      o Total bilirubin > 5 x ULN

      o Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:

  – Grade 4 neutropenia ≤ 7 days

  – Grade 4 lymphopenia or leukopenia

  – Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

  – Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. It is recommended to consult with the Principal Investigator for Grade 4 amylase or lipase abnormalities

  – For Grade 4 endocrinopathy AEs such as adrenal insufficiency, ACTH deficiency, hyper or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered after discussion with the Principal Investigator

- Any dosing interruption lasting > 6 weeks from the last dose with the following exceptions:

– Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing interruption lasting > 6 weeks from the last dose, the Principal Investigator must be consulted

– Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study therapy dosing

Tumor assessments for all participants should continue as per protocol even if study therapy dosing is interrupted.

### 6.5.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The recommendation is to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management across the study.

The algorithms are found in the Nivolumab Investigator Brochure and Appendix 2 of this protocol.

### 6.5.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD)[48]. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any

benefit from continued study therapy. Participants will be permitted to continue treatment beyond initial progressive disease as long as all of the following criteria are met and clearly documented:

- Investigator-assessed clinical benefit and no rapid disease progression;
- Tolerating study drug(s);
- Stable performance status;
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Participant provides written informed consent prior to receiving additional study therapy, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

Additionally, patients who have progressed between screening imaging and baseline imaging (See Table 7.4-1) but prior to initiation of ipilimumab/nivolumab may be allowed to proceed with ipilimumab/nivolumab beyond progression at the investigator's discretion. All decisions to continue treatment beyond initial progression must be discussed with the Principal Investigator and documented in the study records. The participant will continue to receive monitoring according to the Time and Events Schedules in Table 7.1-2 and Table 7.1-3. A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. For the participants who continue study therapy beyond PD, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. For patients with evaluable disease only, further progression is defined as unequivocal disease progression of non-target lesions or the development of new lesions from time of initial PD. Treatment should be discontinued permanently upon documentation of further disease progression. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, participants who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. For participants in all treatment arms, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression (i.e., radiographic confirmation) even after discontinuation of treatment.

### 6.5.6 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Because nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur,

it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Principal Investigator and reported as a serious adverse event (SAE) if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

**For Grade 1 symptoms**: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study therapy administrations

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

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

- The following prophylactic premedications are recommended for future infusions:

  diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study therapy administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilator support indicated).

Immediately discontinue infusion of study therapy. Begin an IV infusion of normal saline and treat the participant as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participants should be monitored until the investigator is comfortable that the symptoms will not recur. Study therapy will

be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids)

## 6.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and CRF.

## 6.7 Destruction or Return of Investigational Product

For this study, IP (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers. If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 10.2.2 for guidance on IP records and documentation.

# 7 STUDY ASSESSMENTS AND PROCEDURES

## 7.1 Flow Chart/Time and Event Schedule

**Table 7.1-1.** Screening Procedural Outline (MCC 18914)[A]

| Procedure | Screening | Notes |
|---|---|---|
| Informed Consent | X | Informed Consent may be obtained at any time, provided it is prior to conduct of any study-related procedures. Note that SAEs are collected from the date of consent. |
| Inclusion/Exclusion Criteria | X | All inclusion/exclusion criteria should be assessed at screening and confirmed prior to study initiation. |
| Medical History | X | |
| Prior Systemic Therapy | X | |
| **Safety Assessments** | | |
| Physical Examination | X | |
| Physical Measurements | X | Include Height, Weight, and ECOG performance Status. Within 28 days prior to thoracic RT. |
| Vital Signs and Oxygen saturation | X | Temperature, BP, HR, and O2 saturation at rest by pulse oximetry. Obtain vital signs at the screening visit and within 72 hours prior to thoracic RT. |
| Assessment of Signs and Symptoms | X | Within 28 days prior to initiation of thoracic RT. |
| Concomitant Medication Collection | X | Within 28 days prior to initiation of Thoracic RT. |
| Laboratory Tests | X | CBC with differential, chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, uric acid, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonates (optional), albumin, amylase, lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) within 28 days prior to initiation of thoracic RT. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing. |
| ECG | X | Within 28 days prior to initiation of thoracic RT. |

| | | |
|---|---|---|
| | | |
| Pregnancy Test | X | Performed within 24 hours prior to initiation of thoracic RT for WOCBP only (serum or urine - local/site). |
| **Efficacy/Biomarker Assessments** | | |
| Radiographic Tumor Assessment | X | Within 28 days prior to initiation of Thoracic RT.<br>---CT/ Chest-With IV contrast preferred.<br>---CT/MRI Abdomen-With oral and IV contrast preferred.<br>---CT/MRI Pelvis-With oral and IV contrast preferred. Only required if patient has known pelvic visceral metastases or bony metastases in the pelvis. ---MRI/CT Brain-with contrast if possible. MRI preferred. |
| Attempt collection of tumor tissue for pathologic confirmation and exploratory biomarker evaluation | X | Although it is not required, a serious attempt must be made to obtain diagnostic tumor tissue for confirmation of small cell pathologic diagnosis and for exploratory endpoints. (FFPE) tumor tissue block or minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Fine needle aspiration is sufficient if that is the only available tissue. Archival tumor material must be made available. |
| Moffitt Cancer Research Network/Clinical Drug Supplies | | |
| Phone calls to MCRN | | Phone calls must be made to MCRN as follows:<br><br>Screening phone call to IVRS: For participant number assignment at the time informed consent is obtained. |
| [A]-Screening Procedure Visit cannot be more than 28 days before initiation of RT | | |

**Table 7.1-2.** On-Treatment Assessments for All Participants, Thoracic Radiation Therapy[A,B]

| Procedure | Radiation Treatments 1-5<br>Beginning of Week 1 | Radiation Treatments 6-10<br>End of Week 2 | Notes |
|---|---|---|---|
| Targeted Physical Examination | X | X | Within 72 hours prior to initiating (Week 1) and after ending (Week 2) thoracic radiation therapy. |
| Vital Signs and Oxygen Saturation | X | X | Temperature, BP, HR, O2 saturation at rest by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to initiating and after ending Thoracic Radiation Therapy and at any time a participant has any new or worsening respiratory symptoms. These can also be used for screening purposes if appropriate. |
| Physical Measurements | X | X | Includes Weight and ECOG performance status within 72 hours prior to dosing. These can also be used for screening purposes if appropriate. |
| Adverse Events Assessment | *CONTINUOUS* | | Assessed using NCI CTCAE v. 4.0. SAEs should be reported within 24 hours through the MCRN protocol outlined in Section 8.1. |
| Review of Concomitant Medications | X | X | |
| Extended Laboratory Tests | X | X | Extended on-study local laboratory assessments should be done within 72 hours prior to initiation of thoracic RT (Week 1) and within 72 hours of completing thoracic RT (Week 2). Labs to be collected include CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. |

| | | | |
|---|---|---|---|
| Thyroid Function Testing | X | | TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (+/-1 week) throughout the study. |
| Pregnancy Test | X | | Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule. |
| **Efficacy Assessments** | | | |
| Radiographic Tumor Assessment | NA | | See Table 7.4-1 and Table 7.4-2 for CT and MRI scan schedule. |
| **Additional Exploratory Biomarker Testing** | | | |
| Serum, Whole Blood Collection | X | X | See Table 7.5-1 for biomarker sampling schedule. |

[A] Thoracic RT start must be at least 3 weeks but not more than 8 weeks after completion of platinum based chemotherapy

[B]Please see section 5.2 for details of RT treatment schedule

**Table 7.1-3.** On-Treatment Assessments for All Participants, Combined Nivolumab and Ipilimumab (Cycle 1 [cycle length = 42 days])[A]

| Procedure | Cycles 1 and 2 | | Notes |
|---|---|---|---|
| | Day 1 | Day 22 | |
| Targeted Physical Examination | X | X | Within 72 hours prior to dosing. |
| Vital Signs and Oxygen Saturation | X | X | Temperature, BP, HR, O2 saturation at rest by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a participant has any new or worsening respiratory symptoms. |
| Physical Measurements | X | X | Includes Weight and ECOG performance status within 72 hours prior to dosing. |
| Adverse Events Assessment | *CONTINUOUS* | | Assessed using NCI CTCAE v. 4.0. SAEs should be reported within 24 hours through the MCRN protocol outlined in Section 8.1. |

| | | | |
|---|---|---|---|
| Review of Concomitant Medications | X | X | |
| Extended Laboratory Tests | X | X | Extended on-study local laboratory assessments should be done within 72 hours prior to dosing on Days 1, 22 and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. |
| Thyroid Function Testing | X | | TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (+/- 1 week). (Day 1 of each Cycle). |
| Pregnancy Test | X | X | Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule. |
| **Efficacy Assessments** | | | |
| Radiographic Tumor Assessment | See Note | | CT chest, CT/MRI abdomen, and any other known or suspected sites of disease. Repeat CT/MRI of pelvis is required for participants with pelvic metastases at baseline, or if clinically indicated. Participants should have surveillance MRI/CT scans of the brain every 12 weeks or sooner if clinically indicated.<br><br>See Table 7.4-1 and Table 7.4-2 for CT and MRI scan schedule. |
| **Additional Exploratory Biomarker Testing** | | | |
| Serum, Whole Blood, Tumor Biopsy | X | X | See Table 7.5-1 for biomarker sampling schedule. |
| **Clinical Drug Supplies** | | | |
| Administer Ipi-3/Nivo-1 | X | X | |

[A]Cycle 1 must start at least 14 days but not more than 21 days after completion of RT

[B] Please see section 6.5.1 for Dosing Windows

**Table 7.1-4.** On-Treatment Assessments for All Participants, Cycle 3 and Subsequent cycles (cycle 3+ length = 28 days)[A,B]

| Procedure | Cycle 3+<br><br>Day 1 | Notes |
|---|---|---|
| Targeted Physical Examination | X | Within 72 hours prior to dosing. |
| Vital Signs and Oxygen Saturation | X | Temperature, BP, HR, O2 saturation at rest by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a participant has any new or worsening respiratory symptoms. |
| Physical Measurements | X | Includes Weight and ECOG performance status within 72 hours prior to dosing. |
| Adverse Events Assessment | *CONTINUOUS* | Assessed using NCI CTCAE v. 4.0. SAEs should be reported within 24 hours through the MCRN protocol outlined in Section 8.1. |
| Review of Concomitant Medications | X | |
| Extended Laboratory Tests | X | Extended on-study local laboratory assessments should be done within 72 hours prior to dosing for Cycle 3 and every cycle thereafter and include: CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. |
| Thyroid Function Testing | X (every 2 cycles) | TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (+/- 1 week) |
| Pregnancy Test | X (every 2 cycles) | Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule. |
| **Efficacy Assessments** | | |
| Radiographic Tumor Assessment | See Note | CT chest, CT/MRI abdomen, and any other known or suspected sites of disease. Repeat CT/MRI of pelvis is required for participants with pelvic metastases at baseline, or if clinically indicated. See Table 7.4-1 and Table 7.4-2 for CT and MRI scan schedule. |
| **Additional Exploratory** | | |

| | | |
|---|---|---|
| **Biomarker Testing** | | |
| Serum, Whole Blood, Tumor Biopsy | See Note | See Table 7.5-1 for biomarker sampling schedule. |
| **Clinical Drug Supplies** | | |
| Administer Nivo 480mg | X | |

[A]Cycle 3 must start at least 42 days but not more than 56 days after completion of Cycle 1 and 2

[B] Please see section 6.5.1 for Dosing Windows

**Table 7.1-5.** Follow-Up Assessments for All Participants (MCC 18914)

| Procedure | Follow-Up Visits 1 and 2[A] | Survival Follow-Up Visits[B] | Notes |
|---|---|---|---|
| **Safety Assessments** | | | |
| Targeted Physical Examination | X | | To assess for potential late emergent study drug-related issues. |
| Adverse Events Assessment | X | X | NSAEs and SAEs must be collected up to 30 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected. SAEs should be reported through the MCRN protocol outlined in Section 8.1. |
| Review of Concomitant Medications | X | X | |
| Extended Laboratory Tests | X | | CBC with differential, uric acid, BUN or serum urea level, creatinine, Na, K, Ca, Mg, phosphorus, chloride, bicarbonate (optional), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH. |
| Thyroid Function Testing | X | | TSH (reflex to free T3 and free T4 if abnormal result). |
| Pregnancy Test | X | | Serum or urine. |

| | | | |
|---|---|---|---|
| **Efficacy Assessments** | | | |
| Radiographic Tumor Assessment | See Note | See Note | See Table 7.4-1 and Table 7.4-2 for CT and MRI scan schedule. |
| **Exploratory Biomarker Testing** | | | |
| Serum, Whole Blood, Tumor Biopsy | See Note | | See Table 7.5-1 for biomarker sampling schedule. |
| **Participant Status** | | | |
| Survival Status | X | X | Every 3 months after follow-up visit 2; may be accomplished by visit or phone contact, to update survival information and assess subsequent anti-cancer therapy. |

[A]-Follow-up visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

[B]-Survival visits continue every 3 months ± 14 days after Follow-up Visit 2 until death, lost to follow-up, or withdrawal of study consent

### 7.1.1 Retesting During Screening

Retesting of laboratory parameters and/or other assessments within the screening period will be permitted (in addition to any parameters that require a confirmatory value). Any new result will override the previous result (i.e., the most current result prior to initiation of thoracic radiation therapy) and is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state. Laboratory parameters and/or assessments that are included in Table 7.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Principal Investigator may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

## 7.2 Study Materials

The following materials will be provided to the site.

- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Imaging and Radiation Planning Manual for image acquisition and submission to central vendor
- Pregnancy Surveillance Forms

## 7.3 Safety Assessments

Safety assessments include AEs, physical examinations, vital signs, ECOG performance status, assessment of signs and symptoms, laboratory tests, pregnancy tests as outlined in Section 7.1.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

### 7.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator as per standard medical/clinical judgment.

## 7.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 7.1. Contrast-enhanced computed tomography (CT) of the chest and CT or magnetic resonance imaging (MRI) of abdomen and any other known or suspected sites of disease are the preferred methods of radiographic assessment of tumors. Repeat CT/MRI of pelvis is required for participants with pelvic metastases at baseline, or if clinically indicated. Brain MRI scan is the preferred imaging method for evaluating CNS metastasis, and assessment is required at screening and every 12 weeks while on study; however, CT of the brain is acceptable if MRI is contraindicated. Patients with incidental asymptomatic brain metastases findings at screening will need to undergo radiation treatment in order to be eligible. Patients are only eligible if according to the clinical judgment of the investigator the finding of an incidental brain metastasis is unlikely to represent progression of disease. The investigator should take results from brain scans at the initial diagnosis into consideration. If a patient has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice.

All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data and should again be used for all subsequent assessments. Bone scan, PET scan, and ultrasound are not adequate for assessment of RECIST 1.1 response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 response. Screening assessments should be performed within 28 days of initiation of radiation therapy . Participants will be evaluated for tumor response outlined in Table 7.4-1 and Table 7.4-2 or more frequently as clinically indicated or per local Standard of Care, until disease progression (or until

discontinuation of study drug in participants receiving study therapy beyond progression), lost to follow-up, withdrawal of study consent, or the study ends. Tumor assessments for all participants should continue as per protocol even if dosing is delayed. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

As outlined in section 9.4.1, progression free survival will be calculated from the date of patient registration. The baseline scan for RECIST 1.1 response evaluation will be the imaging assessment performed 2 weeks after completion of thoracic radiation and prior to C1D1 of combined ipilimumab/nivolumab. If the patient progresses between pre-treatment imaging and the baseline scan prior to initiation of ipilimumab/nivolumab, this will be considered disease progression according to the defined primary endpoint. In this circumstance, at the investigator's discretion, the patient may elect to receive study drugs beyond progression according to section 6.5.5. Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST 1.1 criteria.

**Table 7.4-1.** Schedule of CT/MRI Tumor Assessments [A]

| Time On Study | Assessment Frequency | Assessment Week (Day 1 of Week Shown) | Assessment Window |
|---|---|---|---|
| Screening | | Week 0 | ± 28 days |
| Baseline (RECIST 1.1) | | Week 4 (prior to initiation of ipilimumab/ nivolumab) | +/- 5 days |
| Between Week 10 and Week 35 | Every 8-9 weeks after initiation of Nivolumab/Ipilimumab | 10,19,27,35, | ± 5 days |
| Beyond Week 35 | Every 12 weeks | 47,59,71+, | ± 5 days |

[A]-Acceptable Radiographic Tumor Assessments:
---CT/ Chest-With IV contrast preferred.
---CT/MRI Abdomen-With oral and IV contrast preferred.
---CT/MRI Pelvis-With oral and IV contrast preferred. Only required if patient has known pelvic visceral metastases or bony metastases in the pelvis.

**Table 7.4-2.** Schedule of MRI/CT Brain Surveillance Assessments [A]

| Time On Study | Assessment Frequency | Assessment Week (Day 1 of Week Shown) | Assessment Window |
|---|---|---|---|
| Screening/Baseline | | Week 0 | Within 28 days |
| Week 10 | Every 12-13 | Weeks 10, 23, 35, 47,59+ | ±5 days |

| | | | |
|---|---|---|---|
| | weeks | | |

[A]-MRI/CT Brain-with contrast if possible. MRI preferred.

### 7.4.1 Primary and Secondary Efficacy Assessments

The primary endpoint is progression-free survival at 6 months in all participants. The secondary endpoint is overall survival at 1 year.

See Section 9.4 for the definitions of unacceptable toxicity, OS and PFS. Every effort will be made to collect toxicity, survival and imaging data on all participants, including those withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for additional data collection. If the death of a participant is not reported, all dates in this study representing a date of participant contact will be used in determination of last known date alive.

## 7.5 Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab and ipilimumab will be investigated in tumor specimens obtained at screening and in peripheral blood taken both at screening (prior to initiation of thoracic radiation therapy) and during the study, from all participants as outlined in Table 7.5-1. The de-identified samples will be sent to DiaCarta which is a company that will be performing DNA and RNA sequencing analysis of the peripheral blood specimens we collected for the trial. The de-identified samples will also be sent to Circulogene which is a company that will be performing DNA and RNA sequencing analysis of the peripheral blood specimens we collected for the trial.

**Table 7.5-1.** Biomarker Sampling Schedule for all Participants (MCC 18914)

| Collection Timing[A] | **Serum** | **PBMC** | **Tumor** | **Whole Blood** |
|---|---|---|---|---|
| Study Day | Soluble Biomarkers | Immunopheno-typing | Tumor Biopsy | SNP |
| Screening | | | X[B] | |
| Prior to First Fraction of Thoracic Radiation (0-3 days prior) | X | X | | X |
| After Last Fraction of Thoracic Radiation (0-3 days after) | X | X | | |
| Prior to each dose of ipilimumab/nivolumab or nivolumab therapy | X | X | | |

| | | | | |
|---|---|---|---|---|
| Upon Progression | X | X | | |
| At first Follow-Up after study discontinuation | X | X | | |

[A]Biomarker sampling occurs prior to dosing and can occur up to 4 days prior to dosing. However, if a sample is collected and the dose is subsequently delayed an additional sample should not be collected.

[B]Submission of a tumor sample prior to study initiation is optional.

### 7.5.1 Tumor Tissue Specimens

Archival or recently collected FFPE tumor tissue (in the form of paraffin embedded block of a minimum of 10 unstained slides) will be collected if possible prior to enrollment. Available specimens must be sent at screening to Moffitt Cancer Center for retrospective determination of PD-L1 status using an analytically verified IHC assay. A biopsy sample from participants who experience progression at any time while on treatment is optional but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy. Biopsy samples may be used for the assessments listed below. Tumor tissue collection details are provided in Section 7.5.4.

### 7.5.2 Characterization of Tumor Infiltrating Lymphocytes (TILS) and Tumor Antigens

Immunohistochemistry may be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before and after exposure to therapy. These immunohistochemistry analyses will include, but not necessarily be limited to, the following markers: CD3, CD4, CD8, CD45RO, FOXp3, PD-1, PD-L1 and PD-L2.

### 7.5.3 DNA and RNA Genomic Assessment

DNA or RNA extracted from tumor provided may be participant to whole genome or exome sequencing using next-generation sequencing to identify mutational load and transcriptional expression.

### 7.5.4 Tumor Sample Collection Details

Archival tumor specimens are expected. Pathology report should be provided with tumor samples. For participants without available archival tissue, a new biopsy is not required as long as a pathologic diagnosis of small cell lung cancer has been established. Formalin-fixed paraffin embedded tissue may be evaluated also by fluorescence in situ hybridization (FISH), genetic mutation detection methods, and/or by quantitative polymerase chain reaction (QPCR) for exploratory analyses of prognostic or predictive molecular markers

associated with SCLC (eg, gene mutation, amplification or overexpression), to determine if these factors influence response to ipilimumab and nivolumab. Such analyses will be completed retrospectively and within the scope of informed consent.

If feasible, tumor biopsies or surgical specimens obtained throughout the participant's standard of care treatment course may be obtained. Where appropriate, changes in expression of immunoregulatory proteins may be assessed in these specimens with the consent of the participant.

### 7.5.5 Peripheral Blood Markers

A variety of factors that may affect the immunomodulatory properties and efficacy of nivolumab will be investigated in peripheral blood specimens taken from all participants prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Several analyses may be completed and are described briefly below.

### 7.5.6 Single Nucleotide Polymorphisms (SNPs)

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for Single Nucleotide Polymorphism (SNP) analyses and serve as a reference for tumor mutational profiling, unless restricted by local regulations. These analyses will focus on SNPs within genes associated with PD-1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to ipilimumab/nivolumab and/or with AEs during treatment.

### 7.5.7 Serum Soluble Factors

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of ipilimumab/nivolumab, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors (eg, soluble PD-L1) may be investigated at baseline and during treatment.

### 7.5.8 Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells in whole blood taken from participants at baseline and on treatment and will be analyzed by flow cytometry or other methods (e.g., ELIspot) to assess immune cell activity.

### 7.5.9 Peripheral Blood DNA and RNA Genomic Assessment

DNA or RNA extracted from peripheral blood samples collected throughout the study may be participant to whole genome or exome sequencing using next-generation sequencing to identify mutational load and transcriptional expression.

# 8 ADVERSE EVENTS

NCI CTCAE Version 4.0 will be utilized for identification and grading of all adverse events.

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug. The causal relationship to study drug is determined by a physician and should be used to assess all adverse events. The causal relationship can be one of the following:

- Unrelated: The Adverse Event is *clearly not related* to the investigational agent(s)
- Unlikely: The Adverse Event is *doubtfully related* to the investigational agent(s)
- Possible: The Adverse Event *may be related* to the investigational agent(s)
- Probable: The Adverse Event is *likely related* to the investigational agent(s)
- Definite: The Adverse Event is *clearly related* to the investigational agent(s)

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

The study sponsor, Moffitt Cancer Center ,will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including FDA Code of Federal Regulations 21 CFR Parts 312 and 320. In addition, K08 CA231454-01A1 Grant support will be provided through Moffitt Cancer Center.

## 8.1 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

☐Results in death

☐Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

☐Requires in-patient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)

☐Results in persistent or significant disability/incapacity

☐Is a congenital anomaly/birth defect

☐Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but

are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization.

- Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 8.6 for the definition of potential DILI.)

- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via study drug is an SAE.

- Although pregnancy, overdose, cancer, and potential drug-induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.4 for reporting pregnancies.)

- Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 8.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event)

- elective surgery, planned prior to signing consent

- admissions as per protocol for a planned medical/surgical procedure

- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

### 8.1.1 Serious Adverse Event Collection and Reporting

The Investigator Brochure (IB) contains Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to the study, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure. The investigator must report any SAE that occurs after these time periods and that is believed to be related to the

study or protocol-specified procedure. An SAE report must be completed for any event where doubt exists regarding its seriousness. All SAEs must be reported to BMS Worldwide Safety. The BMS SAE form should be used to report SAEs.

If the investigator believes that an SAE is not related to the study, 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 must 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 (as below) and to the study sponsor, Moffitt Cancer Center, through the MCRN coordinating center within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).

To ensure patient safety, each serious adverse event must be reported to the BMS, the PI and to the MCRN coordinating center within 24 hours of the investigational staff's knowledge. All participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE must be reported by email (affiliate.research@moffitt.org) to the MCRN within 24 hours of discovery.

The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to both :

**SAE Email Addresses:** affiliate.research@moffitt.org , Worldwide.Safety@BMS.com

**SAE Facsimile Numbers:** MCRN 813-745-5666, BMS 609-818-3804

**SAE Telephone Contacts:** 813-745-6993

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, the SAE report must be updated and submitted within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator. Sponsor/investigator will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

## 8.2 Nonserious Adverse Events

A *nonserious adverse event* is an AE not classified as serious.

### 8.2.1 Nonserious Adverse Event Collection and Reporting

NCI CTCAE Version 4.0 will be utilized for grading of all nonserious adverse events.

The collection of nonserious AE information should begin at initiation of the study. Data will be captured in OnCore, Moffitt's Clinical Trials Database. To obtain access to OnCore, the site research staff must complete forms provided by the MCRN Regulatory Coordinator. Once the completed forms are received, the site coordinator will receive DUO access, logon/password, and information on how to access OnCore. The MCRN Coordinating Center will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 8.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the OnCore CRF. All nonserious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## 8.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic using OnCore) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

## 8.4 Pregnancy

If, following initiation of the study, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of study exposure, including during at least 6 half lives after product

administration, the investigator must immediately notify the BMS Worldwide Safety and the Principal Investigator/designee of this event and complete and forward a Pregnancy Surveillance Form within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 8.1.1. An SAE must also be entered into the OnCore system and an email sent to the MCRN (affiliate.research@moffitt.org) and to BMS (Worldwide.Safety@BMS.com) within 24 hours of discovery.

In most cases, the study drugs will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the Principal Investigator within 24 hours of awareness of the pregnancy.

In the rare event that the benefit continuing the study drug is thought to outweigh the risk, after consultation with the study sponsor, the pregnant participant may continue study drug after a thorough discussion of benefits and risk with the participant.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures 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 Pregnancy Surveillance Form.

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

## 8.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 8.1.1 for reporting details).

## 8.6 Potential Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3.No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## 8.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## 8.8 Protocol Monitoring Committee

A Protocol Monitoring Committee (PMC) will be established to provide oversight of safety and

efficacy considerations in the protocol. The PMC meets monthly and reviews accrual, patterns and

frequencies of all adverse events, protocol violations and when applicable, internal audit results.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Lead in Safety Observation

We will utilize 6-9 patient safety lead in as described in the Section 4.1 with a dose-limiting toxicity period of 13 weeks. We will initially enroll 6 patients. If 0 or 1 of 6 patients develops unacceptable toxicity, then we will proceed with the study as outlined below (to accrue an additional 46 patients). If 2 patients develop unacceptable toxicity, we will enroll an additional 3 patients to determine the rate of unacceptable toxicity with 9 patients. If 3 or more patients develop unacceptable toxicity during any portion of the safety lead in phase, we will discontinue the study.

Additionally, we will be continually assessing toxicity throughout the study and if at any time 3 of the first 9 patients or greater than 33% of patients experience unacceptable toxicity within the 13 week safety observation period, we will discontinue the study. Following the 13-week safety observation period, toxicity will be assessed on an ongoing basis for all patients prior to each dose of ipilimumab/nivolumab or nivolumab alone until study completion.

## 9.2 Phase I/II Sample Size Determination

We propose a single arm, non-randomized phase I/II study, with the goal to evaluate efficacy compared to historical controls. Slotman et al. [5] reported a 6-month progression-free survival (PFS) of 24% with platinum-based chemotherapy and thoracic radiation therapy. We would propose to pursue a phase III randomized controlled study if there is a 20% improvement in 6-month PFS with the addition of combined immune checkpoint blockade as part of the proposed clinical study. Therefore, this regimen would be considered not worthwhile to pursue if the true 6-month PFS is 24% or less and worth pursing if the true 6-month PFS is 44% or greater. The trial will use a Simon's 2-stage design[49] with 1-sided 0.05 level type I error and 90% power. The total target sample size is 52 patients. During the 1st stage, 18 patients will be accrued. If 4 or fewer patients have not progressed at 6 months, the study will be closed for futility. However, if at least 5 patients have not progressed at 6 months, then the study will continue to accrue an additional 34 patients. Once the total number of patients has accrued (n=52), then the null hypothesis will be rejected if at least 18 patients have not progressed at 6 months. In order to accommodate censoring, we may increase the total sample size by up to 10% (n=57).

- The final PFS analysis is targeted to occur 6 months after the last participant is enrolled
- The final OS analysis is targeted to occur 1 year after the last participant is enrolled.

### 9.2.1 Accrual Justification

Fifty patients will be included at phase I/II study completion inclusive of those patients treated as part of the safety lead in. Moffitt Cancer Center in Tampa, FL, will be the primary and lead institution for this phase I/II single arm study. Moffitt sees about 40 patients with ED-SCLC each year, and we estimate that approximately 25% of patients will be eligible for study enrollment. Additionally, we have support to enroll patients at up to 5 additional US academic institutions that see a similar number or more patients with ED-SCLC annually. Accounting for delays in study opening at the onset and for delays due to interim safety and efficacy stopping points as described above, we anticipate completing accrual to our 50-patient study in about 18 months. We expect to accrue approximately 1 or 2 patients per month for the first 6 months, then approximately 4 patients per month for the remaining 12 months.

## 9.3 Populations for Analyses - Data Set Descriptions

- **All Treated Participants**: All participants who received at least one dose of any study medication
- **Biomarker Participants**: All participants with available biomarker data

## 9.4 Endpoints

### 9.4.1 Primary Endpoints

***Part I: Safety Run In Phase I***: Unacceptable toxicity status at the end of 13-week safety observation period with unacceptable toxicity defined as:

- Any grade 4 immune related adverse event (irAE),
- Any ≥ grade 3 noninfectious pneumonitis,
- 
- Any grade 3 irAE, excluding pneumonitis, that does not downgrade to grade 2 within 7 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ grade 1 or baseline within 14 days,
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN,
- Any ≥ grade 3 non-irAE, except for the following exclusions:
  - grade 3 fatigue lasting ≤ 7 days
  - grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the participant is asymptomatic
  - grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
  - grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.

***Part II: Phase II*****:** The primary endpoint is 6-month PFS status. PFS is defined as the duration from date of registration to date of first documentation of progression assessed by local investigator or symptomatic deterioration (as defined above) or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

### 9.4.2 Secondary Endpoint

1 year overall survival status: Overall survival (OS) is defined as the duration from date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

### 9.4.3 Exploratory Endpoints

1. Patterns of radiographic response and progression in the thorax, brain, and other sites from the time of small cell lung cancer diagnosis until study conclusion.

2. Patterns of radiographic response and progression within and outside the radiation treatment field from the time of small cell lung cancer diagnosis until study conclusion.

## 9.5 Analyses

### 9.5.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized using descriptive statistics for all participants.

### 9.5.2 Efficacy Analyses

At the PFS analysis time point, primary PFS analyses will be conducted. The PFS curve, PFS median with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

At the OS analysis time point, the OS analyses will be conducted. OS curves, OS medians with 95% CIs, and OS rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

Additionally, at the same time point as the primary OS analysis, PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

### 9.5.3 Safety Analyses

Safety analyses will be performed for all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. The listings by participant will be produced for all deaths, all SAEs, and all AEs leading to discontinuation of study drug. On-study laboratory parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

# 10 STUDY MANAGEMENT

## 10.1 Compliance

### 10.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations per national requirements

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent tothe Study Sponsor, Moffitt Cancer Center through the MCRN Coordinating Center.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

### 10.1.2 Monitoring

Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/ amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

### 10.1.3 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic

signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

## 10.2 Records

### 10.2.1 Records Retention

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; participant's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; participant files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding patient treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

### 10.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority. Moffitt will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### 10.2.3 Case Report Forms

Data will be captured in Oncore, Moffitt's Clinical Trials Database.

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

## 10.3 Clinical Study Report and Publications

The study of these patients and results of all laboratory studies are considered private and confidential. The progress and results of this study will not be presented without approval by the principal investigator.

Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

# 11 LIST OF ABBREVIATIONS

| **Term** | **Definition** |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AIDS | Acquired immunodeficiency syndrome |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AT | Amino transaminases |
| □-HCG | beta-human chorionic gonadotrophin |
| BID,bid | Bis in die, twice daily |
| BMS | Bristol-Myers Squibb |
| BP | Blood pressure |

| | |
|---|---|
| BUN | Blood urea nitrogen |
| C | Celsius |
| Ca++ | Calcium |
| CBC | Complete blood count |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| C1- | Chloride |
| CLcr | Creatinine clearance |
| Cm | Centimeter |
| CNS | Central nervous system |
| CRF | Case Report Form, paper or electronic |
| CTLA-4 | Cytotoxic t lymphocyte-associated antigen 4 |
| dL | Deciliter |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| ED-SCLC | Extensive disease-small cell lung cancer |
| Eg | Exempli gratia(for example) |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FISH | Fluorescent in situ hybridization |
| FSH | Follicle stimulating hormone |
| G | Gram |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyltransferase |
| GFR | Glomerular filtration rate |
| H | hour |
| HbsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HCO3- | bicarbonate |
| HIV | Human Immunodeficiency Virus |
| HR | Heart rate |
| HRT | Hormone replacement therapy |
| ICD | Immunogenic Cell Death |
| ICH | International Conference on Harmonization |
| Ie id | Est (that is) |

| | |
|---|---|
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal products |
| IND | Investigational New Drug Exemption |
| IRB | Institutional Review Board |
| IU | International Unit |
| IU/L | International unit per liter |
| IU/mL | International unit per milliliter |
| IVRS | Interactive voice response system |
| IV | intravenous |
| K+ | potassium |
| Kg | Kilogram |
| KM | Kaplan-meier |
| L | Liter |
| LAM | Lactation amenorrhea method |
| LDH | Lactate dehydrogenase |
| mAB | Monoclonal antibody |
| Mg | Milligram |
| Mg++ | magnesium |

| | |
|---|---|
| Min | Minute |
| mL | Milliliter |
| mmHg | Millimeters of mercury |
| □g | Microgram |
| N | Number of subjects or observations |
| Na+ | Sodium |
| N/A | Not applicable |
| NE | Not evaluable |
| Ng | Nanogram |
| NCCN | National Comprehensive Cancer Network |
| NIMP | non-investigational medicinal products |
| NSCLC | Non small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PD | Pharmacodynamics |
| PD-1 | ProgrammedDeath-1 |
| PD-L1 | Programmeddeath-ligand1 |

| | |
|---|---|
| PD-L2 | Programmeddeath-ligand2 |
| PFS | progression-free survival |
| PR | Partial response |
| PK | Pharmacokinetics |
| PT | Prothrombin time |
| RCC | Renal cell carcinoma |
| RECIST1.1 | Response evaluation criteria in solid tumors version 1.1 |
| RBC | Red blood cell |
| RT | Radiation Therapy |
| SAE | Serious adverse event |
| SCLC | Small cell lung cancer |
| SD | Standard deviation |
| SD | Stable disease |
| SOP | Standard Operating Procedures |
| T | Temperature |
| T | Time |
| TILs | Tumor infiltrating lymphocytes |
| TTR | Thoracic radiation therapy |

| | |
|---|---|
| TSH | Thyroid stimulating hormone |
| ULN | Upper limit of normal |
| WBC | White blood cell |
| WOCBP | Women of childbearing potential |

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# 13 APPENDIX 1: STUDY CALENDAR

| | Screen-ing[A] | W -3 | W -2 | W -1 | W1[B] | W2[C] | W 3 | W4[D] | W 5 | W 6 | W 7 | W 8 | W 9 | W1 0 | W1 1 | W1 2 | W1 3 | W1 4 | W1 5 | W1 6 | W1 7 | W1 8 | W19[E] | W2 0 | W2 1 | W2 2 | W2 3 | W2 4 | W2 5 | W2 6 | W27[+F] | Follow Up[G] | Survival Follow up[H] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical Examination | X | | | | X | X | | X | | | X | | | X | | | X | | | | | | X | | | | X | | | | X | X | |
| Adverse Events Assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Collection | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Review of Concomitant Medications | | | | | X | X | | X | | | X | | | X | | | X | | | | | | X | | | | X | | | | X | X | X |
| Screening Laboratory Tests | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Extended Laboratory Tests | | | | | X | X | | X | | | X | | | X | | | X | | | | | | X | | | | X | | | | X | X | |
| Thyroid Function Testing | X | | | | X | | | X | | | | | | X | | | | | | | | | X | | | | X | | | | X | X | |
| ECG | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test | X | | | | X | | | X | | | X | | | X | | | X | | | | | | X | | | | X | | | | X | X | |
| Simulation for Thoracic Radiation Therapy | X[O] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CT Chest w/ IV contrast[I] | X | | | | | | | X | | | | | | X | | | | | | | | | X | | | | | | | | X | | |
| CT Abdomen w/ IV and oral contrast[J] | X | | | | | | | X | | | | | | X | | | | | | | | | X | | | | | | | | X | | |
| CT Pelvis w/ IV and oral contrast[K] | X | | | | | | | X | | | | | | X | | | | | | | | | X | | | | | | | | X | | |
| MRI Brain w/ IV contrast[L] | X | | | | | | | | | | | | | X | | | | | | | | | | | | | X | | | | | | |
| Attempt collection of diagnostic FFPE tumor tissue[M] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peripheral Blood for Biomarkers[N] | X | | | | X | X | | X | | | X | | | X | | | X | | | | | | X | | | | X | | | | X | X | |
| Administer Thoracic Radiation Therapy | | | | | XXXX X | XXXX X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Administer Ipilimumab 3mg/kg | | | | | | | | X[P] | | | X | | | X | | | X | | | | | | | | | | | | | | | | |
| Administer Nivolumab 1mg/kg | | | | | | | | X | | | X | | | X | | | X | | | | | | | | | | | | | | | | |
| Administer Nivolumab 480mg | | | | | | | | | | | | | | | | | | | | | | | X | | | | X | | | | X | | |

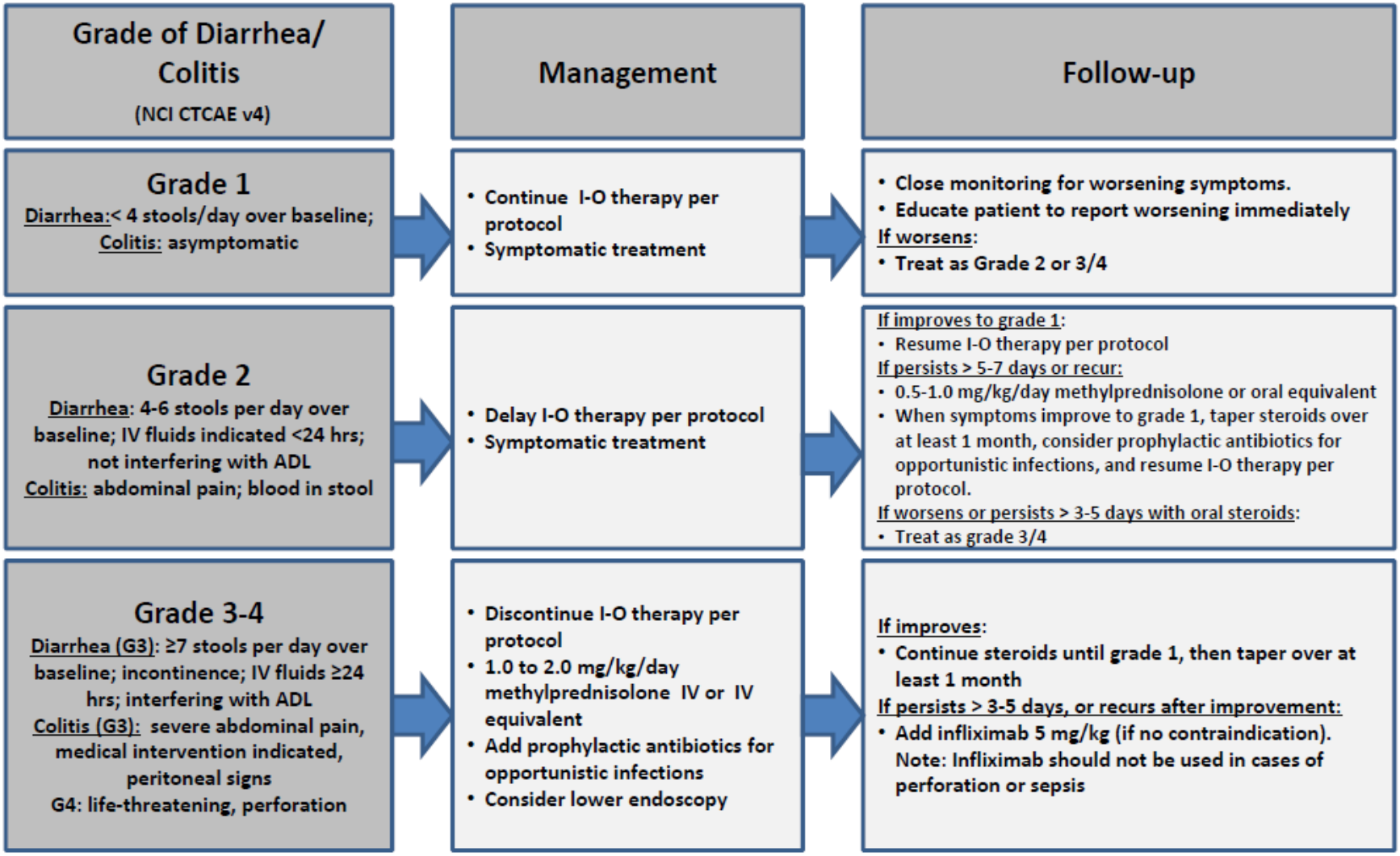
[A] Not more than 28 days before initiation of RT. See Table 7.1-1 for details of screening procedures.
[B] Within 72 hours prior to initiation of RT. See Table 7.1-2 for details of thoracic RT schedule.
[C] Within 72 hours after completing RT. See Table 7.1-2 for details of thoracic RT schedule.
[D] See Table 7.1-3 for details of combined ipilumumab and nivolumab treatment schedule.
[E] See Table 7.1-4 for details of nivolumab alone treatment schedule.
[F] See Table 7.1-4 for detailed instructions related to ongoing assessments with nivolumab maintenance therapy
[G] See Table 7.1-5 for details of follow up after discontinuation of study therapy.
[H] See Table 7.1-5 for details of survival follow up visits.
[K] Required only if patient has known history of pelvic metastases
[L] CT brain w/ contrast acceptable
[M] For exploratory biomarker evaluation (prefer surgical specimen or core biopsy tissue, FNA also acceptable)
[N] See Table 7.5-1 for details of peripheral blood collection for biomarkers
[O] Anytime within 28 days before initiation of RT
[P] Must start more than 14 days but less than 28 days after completion of RT

# 14 APPENDIX 2: MANAGEMENT ALGORITHMS FOR IMMUNE ADVERSE EVENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Principal Investigator.. The guidance applies to all immuno-oncology (I-O) agents and regimens. A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.  The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

# GI Adverse Event Management Algorithm

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

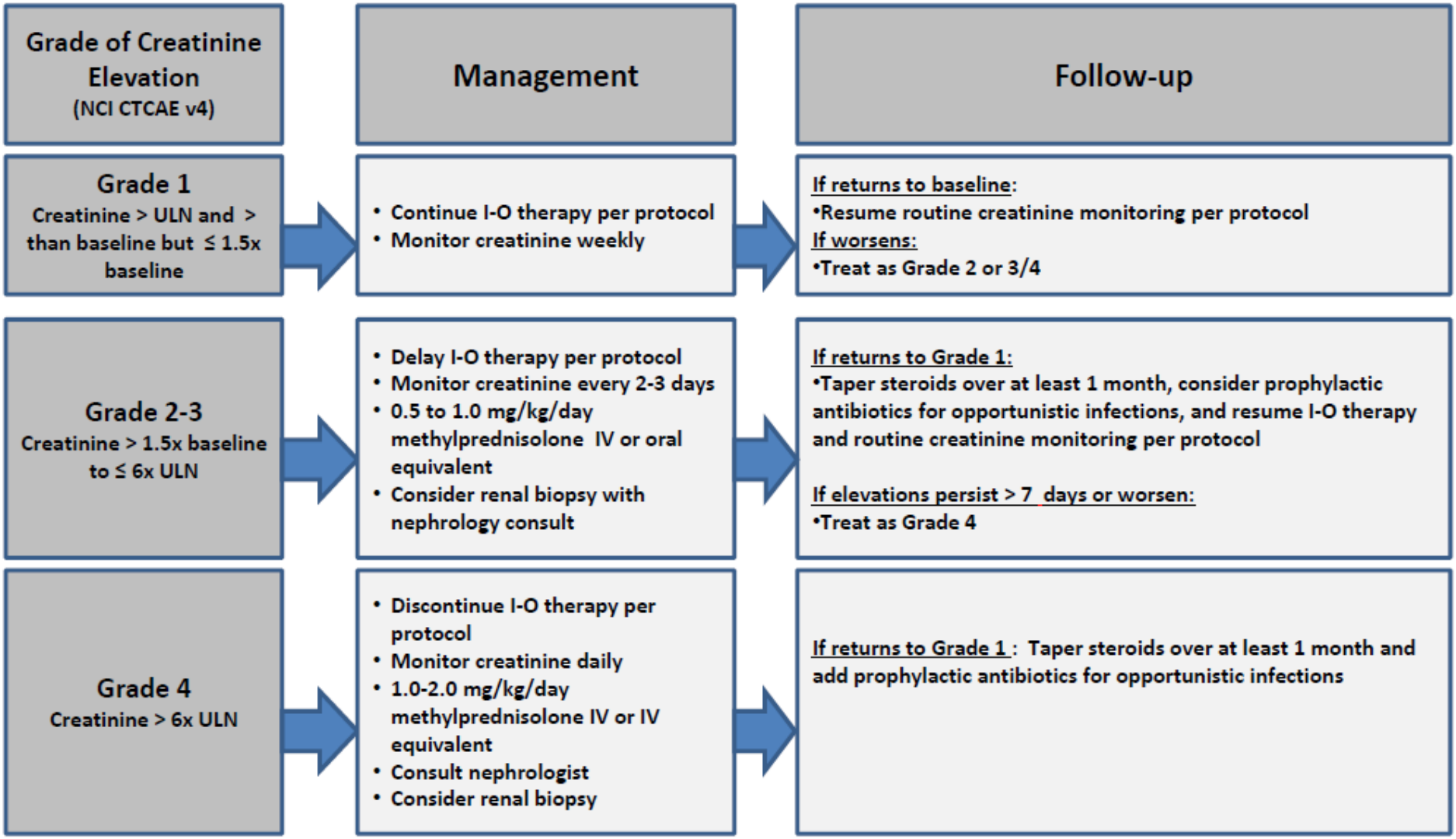



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

# Renal Adverse Event Management Algorithm

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




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

Updated 05-Jul-2016

# Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

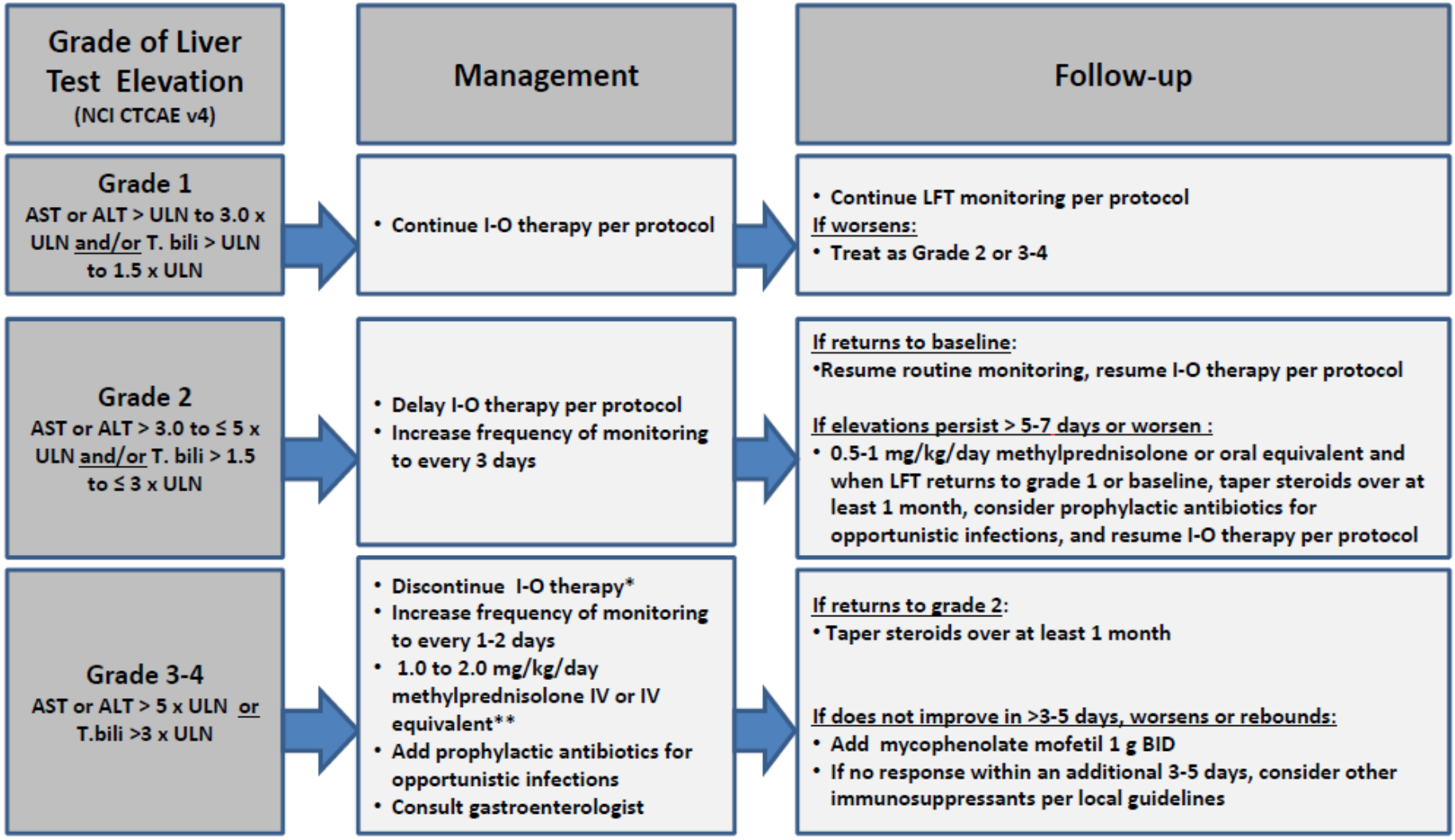
| Grade of Pneumonitis (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>Radiographic changes only | • Consider delay of I-O therapy<br>• Monitor for symptoms every 2-3 days<br>• Consider Pulmonary and ID consults | • Re-image at least every 3 weeks<br>If worsens:<br>• Treat as Grade 2 or 3-4 |
| **Grade 2**<br>Mild to moderate new symptoms | • Delay I-O therapy per protocol<br>• Pulmonary and ID consults<br>• Monitor symptoms daily, consider hospitalization<br>• 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent<br>• Consider bronchoscopy , lung biopsy | • Re-image every 1-3 days<br>If improves:<br>• When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics<br>If not improving after 2 weeks or worsening:<br>• Treat as Grade 3-4 |
| **Grade 3-4**<br>Severe new symptoms; New/worsening hypoxia; Life-threatening | • Discontinue I-O therapy per protocol<br>• Hospitalize<br>• Pulmonary and ID consults<br>• 2-4 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consider bronchoscopy, lung biopsy | If improves to baseline:<br>• Taper steroids over at least 6 weeks<br>If not improving after 48 hours or worsening:<br>• Add additional immunosuppression |

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

Updated 05-Jul-2016

# Hepatic Adverse Event Management Algorithm

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




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

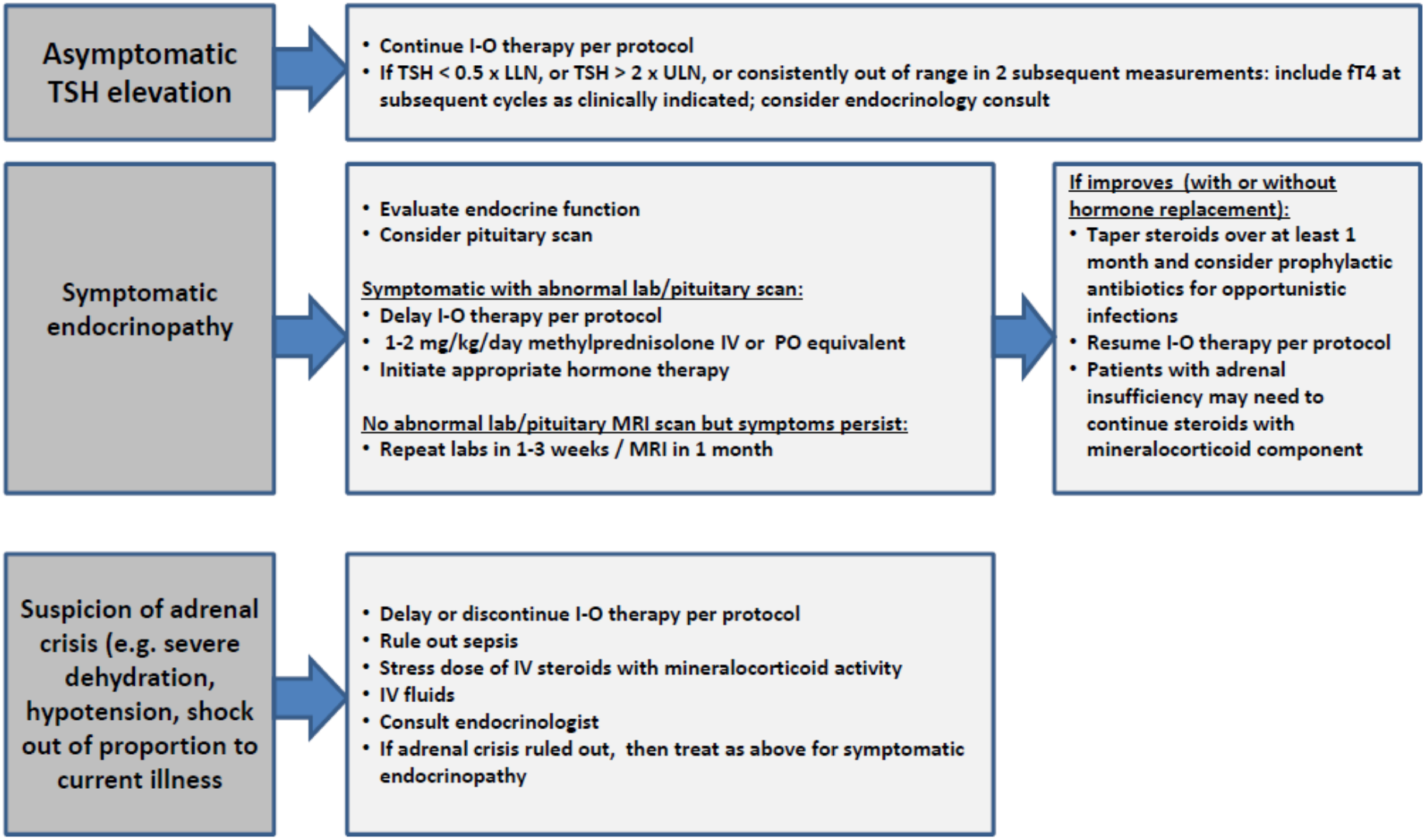
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

# Endocrinopathy Management Algorithm

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

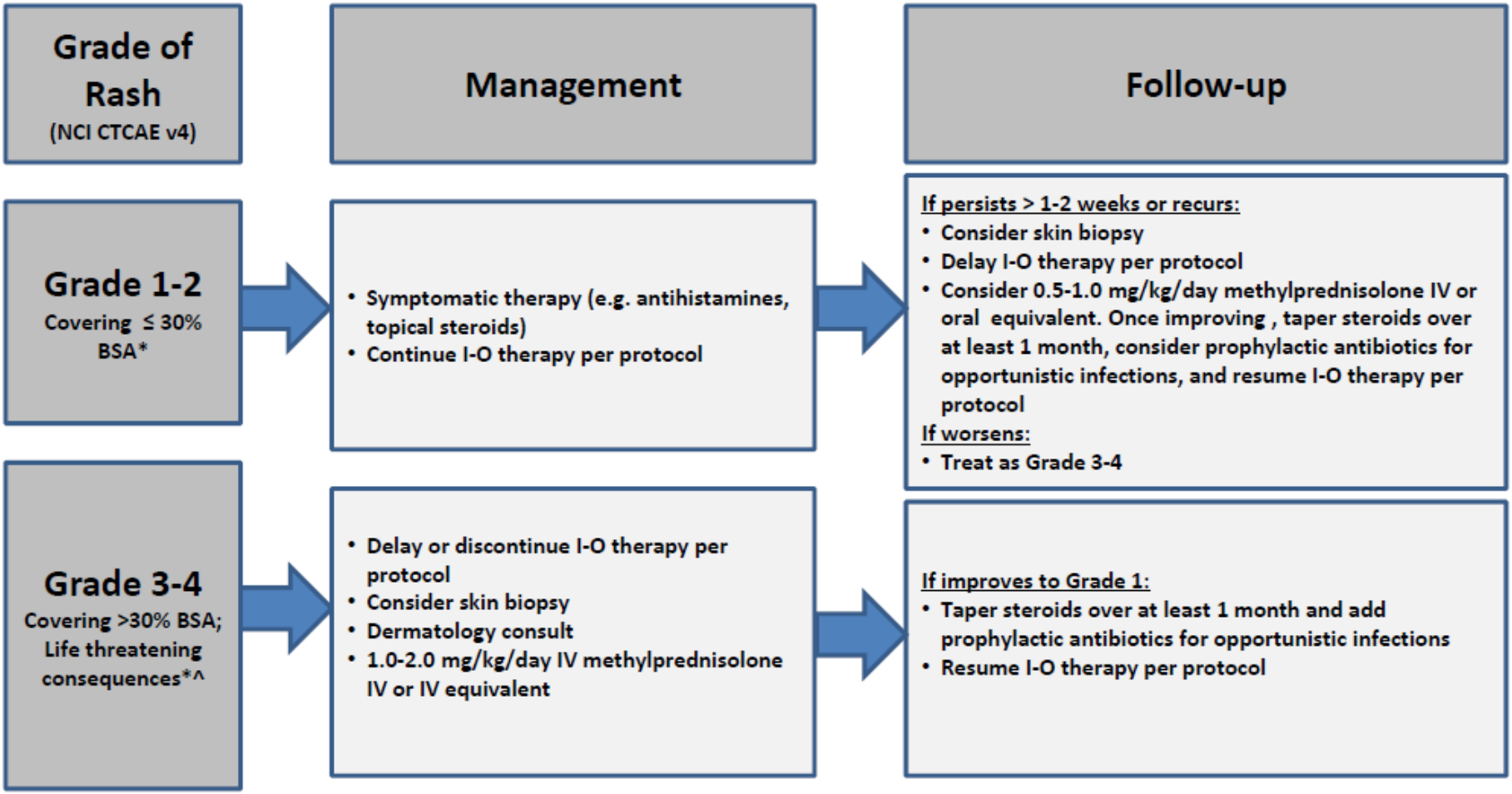



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

# Skin Adverse Event Management Algorithm

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




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

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

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



Updated 05-Jul-2016

# Neurological Adverse Event Management Algorithm

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

| Grade of Neurological Toxicity (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| **Grade 1**<br>Asymptomatic or mild symptoms; Intervention not indicated | • Continue I-O therapy per protocol | Continue to monitor the patient.<br>If worsens:<br>• Treat as Grade 2 or 3-4 |
| **Grade 2**<br>Moderate symptoms; Limiting instrumental ADL | • Delay I-O therapy per protocol<br>• Treat symptoms per local guidelines<br>• Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent | If improves to baseline:<br>•Resume I-O therapy per protocol when improved to baseline<br>If worsens:<br>• Treat as Grade 3-4 |
| **Grade 3-4**<br>Severe symptoms; Limiting self-care ADL; Life-threatening | • Discontinue I-O therapy per protocol<br>• Obtain neurology consult<br>• Treat symptoms per local guidelines<br>• 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections | If improves to Grade 2:<br>• Taper steroids over at least 1 month<br><br>If worsens or atypical presentation:<br>• Consider IVIG or other immunosuppressive therapies per local guidelines |

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

Updated 05-Jul-2016