Radiation and Chemotherapy with Ipilimumab followed by Nivolumab for Patients with Stage III Unresectable NSCLC

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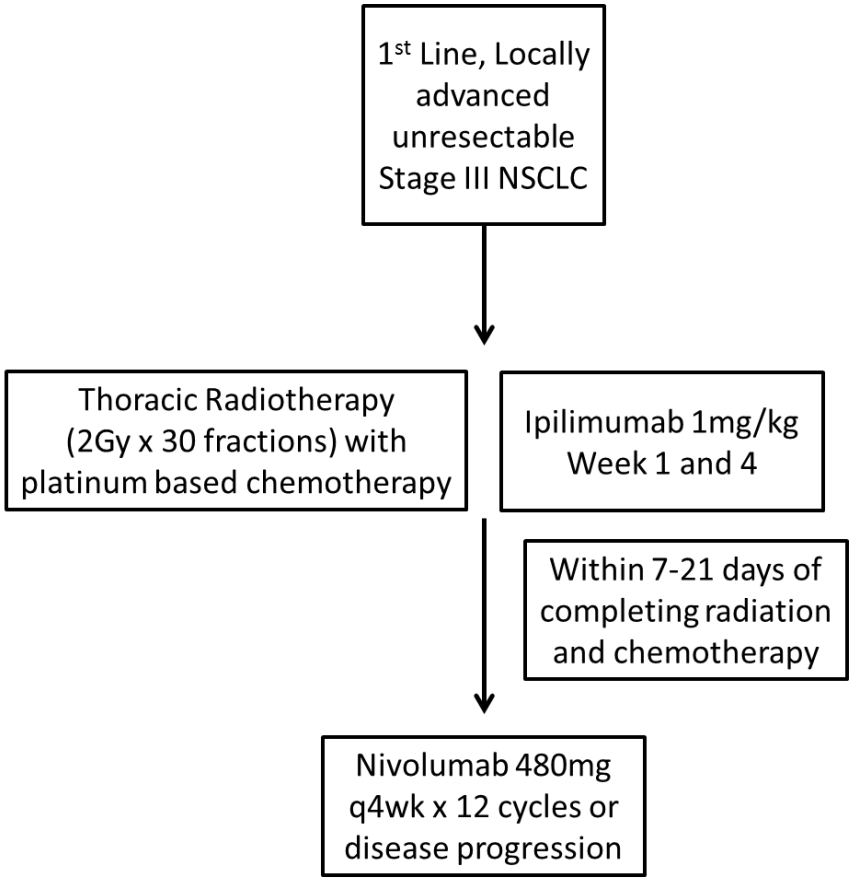
STUDY SYNOPSIS



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1 INTRODUCTION

MCC 19704 is a non-randomized, single-arm, multicenter, phase I/II study in adult patients with unresectable Stage III NSCLC. Fifty participants will be enrolled with the proposed study design. Patients will commence with chemoradiotherapy (60Gy in 30 fractions directed at all sites of suspected disease with concurrent platinum based chemotherapy) with iplimumab delivered concurrently with initiation of chemoradiotherapy and in week 4 of chemoradiotherapy followed by maintenance nivolumab for up 12 cycles or until progression. This study will determine whether the proposed research treatment strategy demonstrates acceptable toxicity and whether the treatment regimen will improve 12-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 study therapy.

1.1 Study Rationale

1.1.1 Rationale for ipilimumab (anti CTLA4) 1mg/kg every 3 weeks for 2 doses in conjunction with chemoradiotherapy

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 [1]. Accumulating evidence indicates that RT can trigger an additional type of cellular demise termed immunogenic cell death (ICD) [2]. 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 [3]. 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 [4]; this effect was found to be dependent on induced DAMP exposure. RT has also been found to increase MHC I expression [5], increase ligands that promote immune activity and enhance the profile of inflammatory soluble mediators in the tumor microenvironment [6]. 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 micrometastatic disease outside of the radiation field may also be affected by the generation of this locally produced *in situ* vaccine. This phenomenon is thought to be mediated by the immune system [7]. 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 [8]. These findings were confirmed in other model systems [9, 10] and subsequent studies demonstrated that RT also increases T cell expansion, DC activation and cytokine release [11].

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 [12]. Also, PD-1 deficient mice or PD-1 blockade lead to an abscopal effect in melanoma and renal cell cancer models [13]. Importantly, these preclinical findings have demonstrated merit in clinical studies. The abscopal effect has been recognized in combination with CTLA-4 blockade in melanoma [14] and NSCLC [15]. 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 [16]. 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 thoracic radiation therapy for NSCLC, 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 [17]. 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 [18]. Additionally, NSCLC patients that received RT followed by nivolumab [19] or a single patient in a case report who received concurrent RT and ipilimumab [15] 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 [16]. Combining RT, which can instigate a robust immune response, with checkpoint inhibition may provide synergism in immune-mediated destruction of NSCLC tumors. By treating Stage III unresectable NSCLC with definitive chemoradiotherapy and ipilimumab followed by nivolumab, improved synergism between RT and immunotherapy may be possible.

Ipilimumab has been shown to induce expansion of the costimulatory T cell response in the lymph node compartments. We hypothesize that ipilimumab in conjunction with chemoradiotherapy may improve the effectiveness of “in situ” vaccine at the onset of treatment for these patients. Various dose and scheduling strategies for ipilimumab with nivolumab have been evaluated across Phase I-III trials in NSCLC. For NSCLC, a dose of 1mg/kg has been generally selected for its favorable toxicity profile with similar efficacy compared to strategies evaluating ipilimumab 3mg/kg dose schedules. Checkmate 227 demonstrated a progression free survival benefit with ipilimumab 1mg/kg every 6 weeks in conjunction with nivolumab 3mg/kg every 2weeks compared to cytotoxic chemotherapy for Stage IV first line NSCLC patients with high mutational burden [20]. The selected dose strategy for this study with ipilimumab 1mg/kg for 2 doses delivered 3 weeks apart is proposed to maximize immune activation during the 6 week chemoradiotherapy course with the addition of ipilimumab. Higher doses of ipilimumab 3mg/kg every 3 weeks have been utilized in other studies combining radiation with ipilimumab[21, 22]. However, a more recent study in metastatic NSCLC suggests that lower doses of ipilimumab 1mg/kg every 6 or even 12 weeks shows similar efficacy a lower dose[23]. Ipilimumab 1mg/kg has been shown to be efficacious utilizing an every 3 week dose schedule for treatment of intermediate or poor risk advanced renal cell carcinoma[24]. In an effort to minimize treatment toxicity with combined

curative intent radiation and cytotoxic chemotherapy, a dose strategy of ipilimumab 1mg/kg every 3 weeks has been selected for our study. Subsequent anti-PD1 therapy with nivolumab limits activated T-cell tolerance following initial immune activation with ipilimumab and chemoradiotherapy and may be essential for limiting metastatic progression.

1.1.2 Rationale for consolidative anti PD-1 therapy after definitive chemoradiotherapy for patients with unresectable Stage III NSCLC

Stage III NSCLC accounts for about 25% of new cases of lung cancer and is associated with poor outcomes. The role of surgery for stage III NSCLC is controversial. For patients with Stage IIIB NSCLC, surgery has not been shown to be beneficial. Consideration of surgical resection should be made in a multidisciplinary fashion for patients with Stage IIIA disease. Patients with unresectable Stage III NSCLC were recently enrolled in a randomized study of chemoradiotherapy followed by anti PD-L1 therapy with durvalumab[25]. Progression free survival was significantly improved for patients randomized to receive durvalumab with limited increased toxicity profile compared to placebo. The FDA has approved durvalumab in the consolidative setting after completion of chemoradiotherapy. Nivolumab is currently being evaluated in unresectable NSCLC population during and after chemoradiotherapy (NCT02434081). Multiple other ongoing clinical studies are evaluating consolidative anti-PD1 therapy for patients with unresectable Stage III NSCLC (NCT02343952, NCT03379441). Anti PD-1/PD-L1 therapy may represent a new standard of care for unresectable NSCLC population after chemoradiotherapy.

1.1.3 Rationale for concurrent platinum based chemotherapy with radiation therapy to a dose of 60Gy

Treatment of Stage III non-small cell lung cancer (NSCLC) has historically consisted of radiation and chemotherapy. RTOG 94-10 was a randomized Phase III study that established concurrent platinum based chemotherapy with cisplatin and vinblastine and radiotherapy to a total dose of 60Gy was superior to a sequential chemotherapy followed by radiation therapy approach[26]. A meta-analysis further demonstrated the benefits of concurrent platinum based chemotherapy with radiation for patients with Stage III unresectable NSCLC[27]. Most recently, a two by two factorial design phase III randomized controlled study evaluated 60Gy vs 74Gy dose and consolidative cetuximab vs no consolidative cetuximab for patients with unresectable Stage IIIA or Stage IIIB NSCLC[28]. Interestingly, Bradley's study found that patients who received 60Gy radiation therapy had outcomes which may have been superior patients receiving 74Gy. There was no difference in the estimated median progression free survival when comparing the 60Gy study arm (11.8 months) and the 74Gy arm (9.8 months). In fact, median overall survival was only 20.3 months in the 74Gy arm compared to 28.7 months in the 60Gy arm. There was no difference in primary outcomes with consolidative cetuximab.

Multiple subsequent studies have attempted to evaluate various consolidative therapies with minimal success[29-31] until the PACIFIC study[25] showed a significant progression free survival benefit with durvalumab as discussed in section 1.1.2. Antonia et al utilized a strategy that recommended 54-66Gy radiation therapy concurrent with platinum based chemotherapy as outlined in our study design.

1.1.4 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 [32] and also in combination with ipilimumab [33]. 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.

1.3 Research Hypothesis

For patients with unresectable Stage III NSCLC, we hypothesize that ipilimumab with thoracic radiation therapy (60 Gy in 30 fractions) followed by nivolumab monotherapy every 4 weeks for up to 12 months will improve 12-month PFS by at least 15% compared with a 12-month historical PFS rate of 49%[28] among patients treated in a similar fashion with concurrent chemoradiotherapy.

1.4 Overall Risk/Benefit Assessment

Stage III unresectable NSCLC is a disease with high unmet medical need. Despite robust initial response rates to concurrent chemoradiotherapy regimens, subsequent progression is typically rapid and overall survival rates are poor. The PACIFIC study established a progression free survival benefit for consolidative anti PD-L1 therapy after chemoradiotherapy for patients with unresectable Stage III NSCLC. The addition of ipilimumab with chemoradiotherapy may lead to improved systemic anti-tumor response with consolidative anti PD-1 therapy.

Concurrent chemoradiotherapy with ipilimumab can cause clinically relevant AEs, including esophagitis, pneumonitis, liver toxicities, thyroiditis, 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 an 8-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 Stage III NSCLC.

2 OBJECTIVES

2.1 Primary Objective

2.1.1 Part 1: Safety Run In

To confirm the recommended phase II dose of ipilimumab with chemoradiotherapy followed by nivolumab for patients with Stage III NSCLC.

2.1.2 Part 2: Phase II

To estimate the 12 month **progression free survival** among patients with unresectable Stage III NSCLC treated with ipilimumab with chemoradiotherapy followed by nivolumab.

2.2 Secondary Objectives

-To estimate the median **overall survival** among patients with Stage III NSCLC treated with ipilimumab with chemoradiotherapy followed by nivolumab..

-To estimate the median **distant metastasis free survival** among patients with Stage III NSCLC treated with ipilimumab with chemoradiotherapy followed by nivolumab..

-To estimate the **objective response rate (ORR)** among patients with Stage III NSCLC treated with ipilimumab with chemoradiotherapy followed by nivolumab. The best objective response (BOR) will also be reported.

-To estimate the **Duration of Response (DOR)** among patients among patients with Stage III NSCLC treated with ipilimumab with chemoradiotherapy followed by nivolumab.

2.3 Exploratory Objectives

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

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

-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 of 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 for each of the platinum doublet chemotherapy options as described in the Section 9.1 with a safety observation period of 8 weeks after initiation of chemoradiotherapy. For each of the proposed platinum doublet chemotherapy combinations, we will initially enroll 6 patients and wait until completion of the 8-week safety observation period following initiation of ipilimumab with chemoradiotherapy combination treatment. For each allowed doublet combination, no additional patients will be enrolled until the safety lead in phase is complete. The study may proceed to Phase II once at least one platinum doublet combination has been deemed safe. Only platinum doublet combinations which have been demonstrated as safe concurrent with radiotherapy and ipilimumab during the safety lead in will be allowed in the Phase II expansion.

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 8-week safety observation period, we will discontinue the study. After the 8-week safety observation period, toxicity will be assessed on an ongoing basis for all patients prior to each dose of ipilimumab or nivolumab until study completion. If unacceptable toxicity occurs outside the 8 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 unresectable Stage III NSCLC. Patients will commence with chemoradiotherapy (60Gy in 30 fractions directed at all sites of suspected disease with concurrent platinum based chemotherapy) with iplimumab delivered concurrently with initiation of chemoradiotherapy and in week 4 of chemoradiotherapy followed by maintenance nivolumab for up 12 cycles or until progression . The study design schematic is presented in Figure 4.2-1.

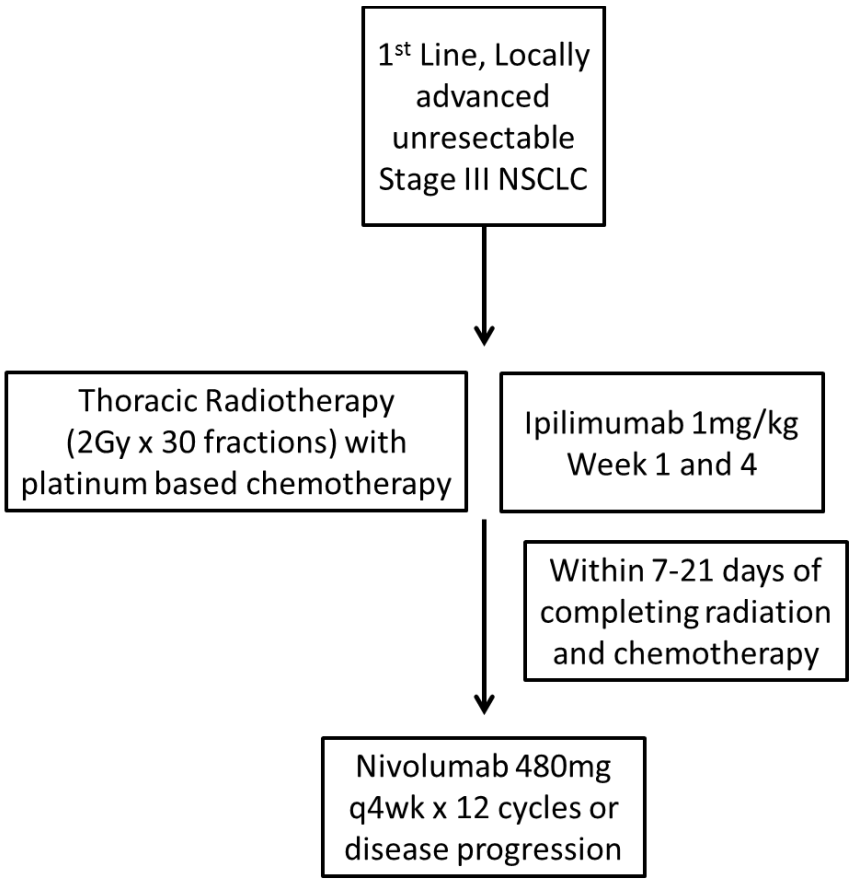

Figure 4.2-1. Study Schematic

The treatment regimen is as follows:

Patients who meet the eligibility criteria and wish to participate will initiate ipilimumab monotherapy (1mg/kg) with thoracic radiation therapy with cytotoxic platinum based chemotherapy including cisplatin and etoposide, carboplatin and paclitaxel or cisplatin and pemetrexed (for patients with non-squamous histology). Selection of the platinum doublet chemotherapy is at the discretion of the patient's treating medical oncologist. Two doses of ipilimumab will be delivered 3 weeks apart. The radiation treatment will be targeting all involved disease in the thorax delineated at the discretion of the treating radiation oncologist. Details of the radiotherapy treatment schedule are outlined in Table 5.2-1. At least 7 days after completion but not more than 21 days after chemoradiotherapy, patients will commence nivolumab 480mg (30-minute IV infusion), as described in Table 6.5-1.

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

1) Initiate study therapy with ipilimumab 1mg/kg to be delivered within 48 hours before or after initiating chemoradiotherapy, ideally on the day of chemoradiotherapy initiation. Two doses of ipilimumab will be delivered 3 weeks apart.

2) Patients will commence with chemoradiotherapy including thoracic radiation to a dose of 60Gy in 2Gy daily fractions. Systemic cytotoxic chemotherapy will be a platinum based doublet regimen consisting of cisplatin and etoposide, carboplatin and paclitaxel, or cisplatin and pemetrexed (for

patients with non-squamous histology) as outlined in table 6.5-1 at the discretion of the treating medical oncologist.

3) Seven to twenty-one days after completion of chemoradiotherapy, initiate maintenance nivolumab delivered every 4 weeks at a dose of 480 mg/cycle for up to 12 cycles.

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

On-study tumor assessments commence after completion of chemoradiotherapy no more than 14 days before the first dose of consolidative nivolumab monotherapy. 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 42 months (18 months of accrual + 24 months of follow-up), assuming an increasing accrual rate from 2 participants/month for the first 6 months, then increasing accrual rate (4 participants/month during remaining 16 months). 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.

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. If a recent tumor biopsy has not been performed, it is required before enrolling on the study.

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

- 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 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 NSCLC.

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.

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 NSCLC including both squamous and non-squamous subtypes documented by histology or cytology from brushing, washing, or needle aspiration of a defined lesion, but not from sputum cytology alone; patients with a known targetable EGFR or ALK mutation will be eligible.

b) Participants must have presented at initial diagnosis with Stage III disease according to AJCC Cancer Staging Manual, 8th Edition;

c) Participants must be deemed by the treating investigator to be surgically unresectable. Ideally, each patient's case will be discussed by the institution's multidisciplinary board, consisting of at least 1 thoracic surgeon, radiation oncologist, and medical oncologist with expertise in the treatment of lung cancer.

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

e) Participants must initiate study treatment 60 days from the date of pathologic diagnosis;

f) Tumor biopsy specimen including at least formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or up to 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation must be available for submission to the central lab for correlative studies;

f) 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 14 days prior to the start of thoracic radiation therapy;

c) Women must not be breastfeeding;

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. Azoospermic males are exempt from contraceptive requirements;

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

f) 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;

g) 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 who have received no more than 1 prior cycle of induction platinum based chemotherapy may be enrolled at the discretion of the treating investigator.

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 $\leq$ 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) Prior history or active pneumonitis, interstitial lung disease that required corticosteroids or that is symptomatic or may interfere with the detection or management of suspected drug and/or radiationrelated 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, including, but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, history of myocardial infarction or cerebrovascular accident or transient ischemic attacks within 6 months from initiation of study drug, uncontrolled seizures or psychiatric illness/social situations that would limit compliance.

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

j) Patients may not have received a live attenuated vaccination within 30 days of starting study 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) < $1500/mm^3$.

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

iii) Hemoglobin level < 9.0 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

f) Inadequate renal function defined as:

Calculated creatinine clearance (CrCl) of < 60 mL/min (Cockcroft-Gault formula)

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 that is not designated as part of the study protocol (ie, chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for the treatment of cancer);
- Supplemental oxygen therapy
- Surgical resection of tumor;

4.5.2 Other Restrictions and Precautions

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

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. 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 initiation is encouraged.

4.6 Discontinuation of Participants Following Any Study Treatment

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 participant 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 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 60 Gy will be given in 30 daily fractions of 2 Gy prescribed to the planning target volume (PTV) with at least 95% of the PTV receiving 60 Gy. An acceptable variation is at least 90% of the PTV receiving 60 Gy. The maximum dose for any contiguous volume of no more than 0.03 cc inside the PTV must not exceed 115% of the prescribed dose. An acceptable deviation is a maximum dose inside the PTV of up to 120% of the prescribed dose. The minimum dose (0.03 cc) to the PTV volume should be no less than 57Gy. An acceptable deviation is a minimum PTV dose of 55.8Gy. 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 30 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 > 3 days should be reported to the principal investigator.

Table 5.2-1. Radiation Treatment Schedule

Thoracic RT Planning Simulation	**Radiation Treatments 1-30**
Between Day -21 and Day 0	Cycle 1, Days 1-42, (generally Monday-Friday)

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 involved intrathoracic disease contoured as GTV plus 0-1cm (preferable 0.6-0.8cm) expansion volume accounting for anatomic boundaries. Additionally, the CTV volume will include any involved SC, hilar or mediastinal lymph node sites that are considered by the treating radiation oncologist to be involved at the time of initial diagnosis. 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 required.

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.

Treatment Planning Technique:

The PTVs are to be treated with an advanced radiation planning technique such as 3D conformal radiotherapy, IMRT, VMAT to deliver the specified dose while restricting the dose to normal tissues. 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 or volumetric arc therapy is allowed at the discretion of the treating radiation oncologist.

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	60Gy >= 95%	60Gy > =90%	60Gy < 90%
	Min (0.03cc) > =57Gy	Min (0.03cc) > =55.8Gy	Min (0.03cc) < 55.8Gy
	Max (0.03cc) <= 69Gy	Max (0.03) <= 72Gy	Max (0.03) > 72Gy
Lungs	V20Gy <= 31%	V20Gy <= 35%	V20Gy > 35%
	Mean < =19Gy	Mean < =20Gy	MLD > 20Gy
Spinal cord	Max (0.03cc) < =52Gy		Max (0.03cc) > 52Gy
Heart	Max(0.03cc)<=66Gy	Max(0.03cc)<=69Gy	Max(0.03cc)>69Gy
	Mean < =26Gy	Mean <= 34Gy	Mean > 34Gy
	V45Gy < =40%	V45Gy <= 66%	V45Gy > 66%

Esophagus	Max(0.03cc)<=66Gy	Max(0.03cc)<=69Gy	Max(0.03cc)>69Gy
	Mean < =34Gy	Mean > 34Gy	
	V50Gy < =40%	V50Gy > 40%	
Stomach	Max(0.03cc)<=56Gy	Max(0.03cc)<=60Gy	Max(0.03cc)>60Gy
	V45Gy<15%		V45Gy>15%
Liver	> 700 cc <= 10 Gy	> 700 cc < =18 Gy	< 700 cc <= 18 Gy

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.

Prioritization for targets and organs at risk (for unacceptable deviation):

1. Spinal cord
2. Stomach
3. Lungs
4. PTV
5. Heart
6. Esophagus
7. Liver

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 unless using GITV
GITV	Gross Internal Tumor Volume (*if using ITV approach) Optional
CTV	Clinical Target Volume Required - unless using CITV
CITV	Clinical Internal Target Volume (*if using ITV approach) Optional
PTV	Planning Target Volume

	Required
Lungs	Right Lung + Left Lung minus GTV Required
Heart	Heart/Pericardium Required
Esophagus	Esophagus Required
Spinal Cord	Spinal Cord Required
Non-PTV	External minus PTV Required
Liver	Liver (*if in path of beam) Optional
Stomach	Stomach (*if in path of beam) 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. The treating radiation oncologist, should discuss the case with the Radiation Oncology Principal investigator in circumstances requiring unacceptable deviations. 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 MCC19704

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	IP	200 mg (5	40 mL/vial (4	Store at 2-8°C;

Injection		mg/mL)	vials/carton)	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:

- Ipilimumab
- Nivolumab

6.2 Non-investigational Product

Platinum based chemotherapy with cisplatin and etoposide or carboplatin and paclitaxel will be dosed and delivered utilizing standard of care procedures at the treating institution. For patients with non-squamous histology, cisplatin and pemetrexed is also an acceptable platinum based chemotherapy. Selection of the platinum doublet chemotherapy is at the discretion of the treating medical oncologist. Recommended dose schedules are outlined in in table 6.5-1 however dose de-escalations, transitioning from cisplatin to carboplatin and holding platinum based chemotherapy is at the discretion of the treating investigator according to standard of care policies. Dose and administration details for platinum-based chemotherapy for each patient will be collected as part of the study. 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>
<tr><td colspan="2">Table 6.5-1. Dosing Schedule (Cycles 1-2+)</td></tr>
<tr><td>Cycle 1 Ipilimumab with Radiation and Chemotherapy

(49-day cycle)</td><td>Cycle 2+

(28-day [4 week] cycles)</td></tr>
<tr><td>Days 1, 22: Ipilimumab 1mg/kg IV (further diluted with appropriate diluent to final concentration 1-2 mg/mL)</td><td rowspan="4">Day 1: 480 mg Nivolumab IV (further diluted with appropriate diluent to final concentration 1-10 mg/mL)</td></tr>
<tr><td>Day 1-42: Radiation therapy, 5 days per week M-F</td></tr>
<tr><td>**Selection of one of the platinum doublet chemotherapy combinations below is at the discretion of the treating medical oncologist.
Days 1, 8, 29 and 36: Cisplatin 50mg/m^2 IV
+
Days 1–5 and 29–33: Etoposide 50mg/m^2 IV

OR

Days 1, 8, 15, 22, 29, 36: Paclitaxel 50mg/m^2 IV + carboplatin AUC 2mg • min/mL IV

OR

FOR NON-SQUAMOUS HISTOLOGY ONLY
Day 1 and 22: Cisplatin 75 mg/m^2 IV
+
Day 1 and 22: Pemetrexed 500 mg/m^2 IV</td></tr>
</table>

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.

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 Cycle 1:

• Participants may be dosed with ipilimumab 1 mg/kg with no less than 19 days between dose 1 and 2.

During Cycle 2 and beyond:

• Participants may be dosed no less than 26 days from the previous dose of nivolumab

Participants may be dosed up to 5 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. Study visits are to be presumably performed on the same day as study drug administration however study visits may occur up to 7 days before or after planned study drug administration date. Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

6.5.2 Study Medications

Ipilimumab 1 mg/kg will be administered every 3 weeks for 2 doses, followed by nivolumab 480 mg every 4 weeks. The schedule of investigational treatments is divided into 1 prolonged cycle including 2 doses of ipilimumab and standard of care chemoradiotherapy, followed by ongoing 4-week cycles of nivolumab. 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

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 esophagitis and 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 or resolving Grade 2 esophagitis or dysphagia

- 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 esophagitis attributable to chemoradiotherapy does not require treatment discontinuation.

– 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:

- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- 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 missed dose of study therapy 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)[33]. 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

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 Ipilimumab- or Nivolumab-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 5.0) 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[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 initiating study therapy.
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 initiating study therapy.
Assessment of Signs and Symptoms	X	Within 28 days prior to initiation of study therapy.
Concomitant Medication Collection	X	Within 28 days prior to initiation of study therapy.
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 study therapy.
Pulmonary Function Tests (including FEV1 and DLCO)	X	Within 28 days prior to initiation of study therapy.
Pregnancy Test	X	Performed within 14 days prior to initiation of study therapy for WOCBP only (serum or urine - local/site).
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment	X	Within 45 days prior to initiation of study therapy. ---CTChest/Abdomen -With IV contrast preferred. ---PET-CT from skull base to mid thigh (bone scan with CT chest/abdomen/pelvis acceptable) ---MRI/CT Brain-with contrast if possible. MRI preferred.

Pathologic tumor tissue for pathologic confirmation and exploratory biomarker evaluation	X	All patients must have diagnostic tumor tissue for confirmation of non-small cell lung cancer pathologic diagnosis and for exploratory endpoints. Central review of the pathology slides before study enrollment is not required. (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: 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, Cycle 1 (Cycle 1 length = 49 days)[A]

Procedure	Cycle 1, Day 1	Cycle 1, Day 22	Notes
Targeted Physical Examination	X	X	Within 72 hours prior to ipilimumab dose 1 and 2
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 ipilimumab dose 1 and 2 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 ipilimumab dose 1 and 2. These can also be used for screening purposes if appropriate.
Adverse Events Assessment	*CONTINUOUS*		Assessed using NCI CTCAE v. 5.0. 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 ipilimumab dose 1 and 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	X	TSH (reflex to free T3 and free T4 if abnormal result) to be performed within 72 hours prior to ipilimumab dose 1 and 2.
Pregnancy Test	X	X	For WOCBP, serum or urine within 14 days prior to ipilimumab dose 1 and 2
Efficacy Assessments			
Radiographic Tumor Assessment	NA		See Table 7.4-1 for CT scan schedule.
Additional Exploratory Biomarker Testing			
Serum, Whole Blood Collection	X	X	See Table 7.5-1 for biomarker sampling schedule.
Treatment Interventions			
Platinum Based Chemotherapy	X	X	See Table 6.5-1 for details of standard of care, platinum based chemotherapy administration
Thoracic Radiotherapy	X	X	30 daily doses, Day 1-42 (typically M-F)
Ipilimumab 1mg/kg	X	X	Day 1 and Day 22

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

Table 7.1-3. On-Treatment Assessments for All Participants, Cycle 2 and Subsequent cycles (cycle 2+ length = 28 days)[A,B]

Procedure	**Cycle 2+ 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. 5.0. 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	TSH (reflex to free T3 and free T4 if abnormal result) to be performed with each cycle
Pregnancy Test	X	Serum or urine within 14 days prior to each dose for WOCBP.
Efficacy Assessments		
Radiographic Tumor Assessment	See Note	CT chest, CT/MRI abdomen, CT/MRI of pelvis is required for participants with suspected pelvic metastases, or if clinically indicated. See Table 7.4-1 for CT/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 2 may start 7 days after the last dose of thoracic radiotherapy but (Target = 10 days) not more than 21 days after the last dose of thoracic radiotherapy

[B] Please see section 6.5.1 for Dosing Windows

Table 7.1-4. Follow-Up Assessments for All Participants

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 must be collected up to 30 days after study drug discontinuation. SAEs should be collected up to 100 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 for WOCBP.
Efficacy Assessments			
Radiographic Tumor Assessment	See Note	See Note	See Table 7.4-1 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 suspected sites of disease are the preferred methods of radiographic assessment of tumors. PET-CT should be used as the diagnostic staging test of choice whenever possible at the time of screening. This is the preferred test for staging because of its improved ability to detect bone metastases and because it is useful to identify potentially involved hilar and mediastinal sites. In the event, that PET-CT is not available, a bone scan is an acceptable alternative in conjunction with a CT or MRI of the chest, abdomen and pelvis with IV contrast. CT/MRI of pelvis is required as clinically indicated. Brain MRI scan is the preferred imaging method for evaluating CNS metastasis and assessment is required at screening; however, CT of the brain is acceptable. 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.

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. Screening assessments should be performed within 28 days of initiation of study 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 up to 45 days before initiation of study therapy.

Table 7.4-1. Schedule of CT/MRI Tumor Assessments

Time On Study	**Approximate Assessment Week (Day 1 of Week Shown)**	**Assessment Window**
Screening [A]	Week 0	Up to 45 days prior to initiation of ipilimumab
Before Nivolumab [B]	~Week 8 (prior to nivolumab)	Up to 14 days prior to nivolumab dose
With every 3rd Nivolumab cycle, then every 12 weeks until progression or 24 months [B]	~Week 20, 32, 44, 56+	± 5 days

[A]-Acceptable Screening Radiographic Tumor Assessments:
---CT Chest/Abdomen -With IV contrast preferred.
---FDG PET-CT from skull base to mid thigh preferred (Bone Scan + CT chest/abdomen/ pelvis with contrast acceptable)
---MRI Brain -with contrast if possible preferred (CT brain with contrast acceptable) [B]-Acceptable On Study Radiographic Tumor Assessments:
---CT Chest-With IV contrast preferred.
---CT/MRI Abdomen-With IV contrast preferred.
---CT/MRI Pelvis-With IV contrast preferred (for patients with disease in the pelvis)

7.4.1 Primary and Secondary Efficacy Assessments

The primary endpoint is progression-free survival at 12 months in all participants. The secondary endpoint is overall survival at 24 months.

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. Patient samples will be stored for up to 5 years after completion of the study protocol. Participation in exploratory biomarker research is optional and patients can choose whether to participate as part of the informed consent process. Participants may also choose to withdraw their samples from biomarker research at any time. Samples will be stored with a unique study patient identifier and the date and time of specimen collection. If any information is learned from future biomarkers research which could impact participant future health, study doctor will contact participant to share this information. Study identifiers will be linked to individual patients to facilitate the proposed biomarker research however protected health information collected as part of the study will be protected in accordance with our institutional policy. At the time of study publication, de-identified biomarker data may be publically shared in accordance with publication rules but this data will have no associated protected health information (PHI). If any research specimens are to be shared with secondary researchers, samples will be de-identified with no PHI data and protected health information will only be shared if necessary in accordance with our institutional procedure.

Table 7.5-1. Biomarker Sampling Schedule for all Participants (MCC 19704)

Collection Timing[A]	**Plasma**	**PBMC**	**Tumor**	**Whole Blood**
Study Day	Soluble Biomarkers	Immunopheno-typing	Tumor Biopsy	SNP
Screening			X[B]	
Prior to first dose ipilimumab and chemoradiotherapy (0-3 days prior)	X	X		X
Prior to 2nd dose of ipilimumab and first 3 doses of nivolumab therapy	X	X		
Upon Progression	X	X	X[C]	
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 required.

[C]Submission of a tumor sample at the time of tumor progression is optional.

7.5.1 Tumor Tissue Specimens

FFPE tumor tissue (in the form of paraffin embedded block of a minimum of 10 unstained slides) will be collected 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 required if archival tissue >60 days from study enrollment. 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 NSCLC (eg, gene mutation, amplification or overexpression), to determine if these factors influence response to study treatment. 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 the study therapy 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 study treatment 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 ofstudy treatment, 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 5.0 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.

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.

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 5.0 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 for each of the possible platinum doublet combinations with a dose-limiting toxicity period of 8 weeks. For each platinum doublet cohort, 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 3 or more patients develop unacceptable toxicity among the first 6 patients, we will discontinue the study. 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 of 9 patients develop unacceptable toxicity, we will not enroll any additional patients with that platinum doublet combination. Patients will be treated according to study protocol and continue to receive study medication during the safety observation period.

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 8 week safety observation period, we will discontinue the study. Following the 8-week safety observation period, toxicity will be assessed on an ongoing basis for all patients and prior to each dose of 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. Bradley et al.[28] reported a 12-month progression-free survival (PFS) of 49% with platinum-based chemotherapy and thoracic radiation therapy to a dose of 60Gy, and 41% at 74 Gy. Based on these results, we will utilize 47% as the historical rate.

. We would propose to pursue a phase III randomized controlled study if there is a 15% improvement in 12-month PFS with the addition of ipilimumab and nivolumab as part of the proposed clinical study. Therefore, this regimen would be considered not worthwhile to pursue if the true 12-month PFS is 62% or less and worth pursing if the true 12-month PFS is 62% or greater. From the Bradley paper, the PFS behaves close to an exponential distribution at least through 24 months. We thus will assume an exponential distribution through 24 months (censoring at 24 months any time > 24 months). Using the one-arm survival calculator from the SWOG-associated Cancer Research and Biostatistics website (https://stattools.crab.org/Calculators/oneArmSurvivalColored.html), a sample of size 50 will have 90% power with a one-sided alpha of 0.10 to detect an exponential survival advantage when the true 12-month survival rate is 62% compared to a control rate of 47%, with uniform accrual for 18 months and minimum of 12 months of follow-up. It should be noted that additional power is gained over time, and that if the follow-up time is increased to 24 months, the power increases to 95%. Correspondingly, the power is 79% if the true 12-month PFS exponential rate is 58%. When half (N=25) of the patients have been enrolled, we will obtain an early estimate of lambda. Study accrual may be suspended for several months (~25 person months are gained for each month that the protocol is suspended, as there are 25 patients on study), or continued, to be determined by the Moffitt Cancer Center Protocol Monitoring Committee, the study investigators and BMS. In order to accommodate censoring, we may increase the total sample size by up to 10% to include a total of 55 patients The final OS analysis is targeted to occur 2 years after the last participant is enrolled.

9.2.1 Accrual Justification

Fifty-five 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 has extensive experience enrolling patients with locally advanced NSCLC on clinical investigator initiated studies utilizing combined immunotherapy strategies. Additionally, we have support to enroll patients at up to 5 additional US academic institutions that see a similar number or more patients with locally advanced Stage III unresectable NSCLC 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 in about 24 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 8-week safety observation period with unacceptable toxicity defined as:

- Any grade 4 immune related adverse event (irAE)
- 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 radiation dermatitis that resolves to Grade ≤ 2 with supportive measures within 14 days
    - grade 3 fatigue lasting ≤ 14 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 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.

- grade ≥ 3 thrombocytopenia without bleeding
- tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to grade ≤ 2 within 6 days

***Part II: Phase II*:** The primary endpoint is 12-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 Endpoints

2 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.

12 month distant metastasis free survival (DMFS) status: DMFS is defined as the duration from date of registration to date of first documentation of distant metastatic progression beyond the primary tumor site as well as regional lymph nodes 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 distant metastatic progression are censored at date of last disease assessment.

-Objective response rate (ORR) at 6 months. ORR is defined as the proportion of all treated subjects whose best overall response is either a complete response or partial response according to RECIST 1.1 criteria. Best objective response (BOR) will also be reportedCR or PR determinations included in the assessment must be confirmed by a consecutive second (confirmatory) evaluation meeting the criteria for response that is performed at least 4 weeks after the criteria for response are first met. When SD is believed to be the best response, it must meet a minimum SD duration of 49 days. Measurements must have met the SD criteria at least once after study entry.

-Duration of Response (DOR) computed only for subjects with a BOR of CR or PR is defined as the number of days between the date of first response and the subsequent date of objectively documented disease progression based on the criteria (RECIST v1.1) or relapse based on IWG, or death due to any cause, if death occurred within 100 days after last dose, whichever occurs first. If death is more than 100 days after last dose, then DOR is censored at the last tumor assessment date. For those subjects who remain alive and have not progressed or received subsequent therapy, duration of response will be censored on the date of last tumor assessment. Subjects who receive subsequent therapy will be censored at the start of subsequent therapy.

9.4.3 Exploratory Endpoints

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

2. Patterns of radiographic response and progression within and outside the radiation treatment field from the time of 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, 12 and 18 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, 24 and 36 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 5.0. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v5.0 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 v5.0 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
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
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

Study Treatment Phase	**Screening**	**Ipilimumab/ Radio-chemotherapy**		**Nivolumab Monotherapy**												**Follow Up[E]**
Study Cycle	**Screening[A] (Within 28 Days)**	**C1 D1[B]**	**C1 D22[B]**	**C2 D1 C,D**	**C3 D1 C**	**C4 D1 C**	**C5 D1 C**	**C6 D1 C**	**C7 D1 C**	**C8 D1 C**	**C9 D1 C**	**C10 D1 C**	**C11 D1 C**	**C12 D1 C**	**C13 D1 C**	
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Medical History	X															
Physical Examination	X															
Adverse Events Assessment	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	X	X	X	X
Screening Laboratory Tests	X															
Extended Laboratory Tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid Function Testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X															
Pulmonary Function Tests (including FEV1 and DLCO)	X															
Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Simulation for Thoracic Radiation Therapy	X															
CT Chest w/ IV contrast[F]	X															
CT Abdomen w/ IV contrast[F]																

PET-CT (skull base to mid thigh)[F]	X															
MRI Brain w/ IV contrast[F]	X															
Adequate diagnostic FFPE tumor tissue[G]	X															X
Peripheral Blood for Biomarkers[H]		X	X	X	X	X										X
Administer Thoracic Radiation Therapy		X	X													
Administer Ipilimumab 1mg/kg		X	X													
Administer Nivolumab 480mg				X	X	X	X	X	X	X	X	X	X	X	X	

[A] Not more than 28 days before initiation of study therapy, except screening radiographic studies which may be up to 45 days before initiation of study therapy. See Table 7.1-1 for details of screening procedures.

[B] Within 72 hours prior to initiation of ipilimumab. See Table 7.1-2 for details of Cycle 1 schedule.

[C] Within 72 hours prior to initiation of nivolumab. See Table 7.1-3 for details of Cycle 2+ schedule.

[D] Nivolumab must start at least 7 days but not more than 21 days after completion of chemoradiotherapy.

[E] See Table 7.1-4 for details of follow up after discontinuation of study therapy.

[F] See Table 7.4-1 for details of radiographic imaging schedule, Bone scan with CT chest/abdomen/pelvis with contrast is acceptable in place of PET-CT.

[G] For exploratory biomarker evaluation (prefer surgical specimen or core biopsy tissue, FNA also acceptable). Required at study initiation, optional at time of progression.

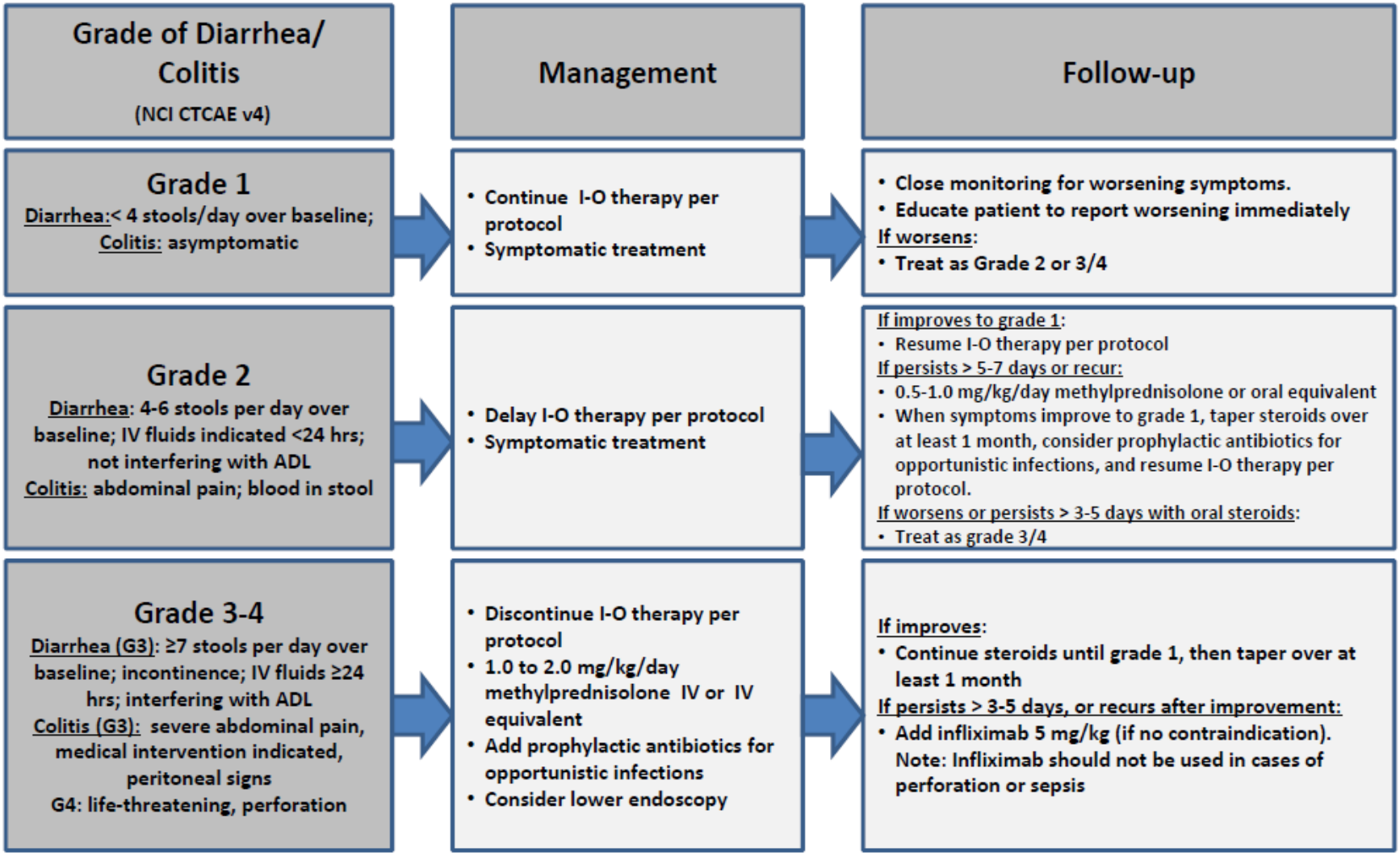
[H] See Table 7.5-1 for details of peripheral blood collection for biomarkers

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.

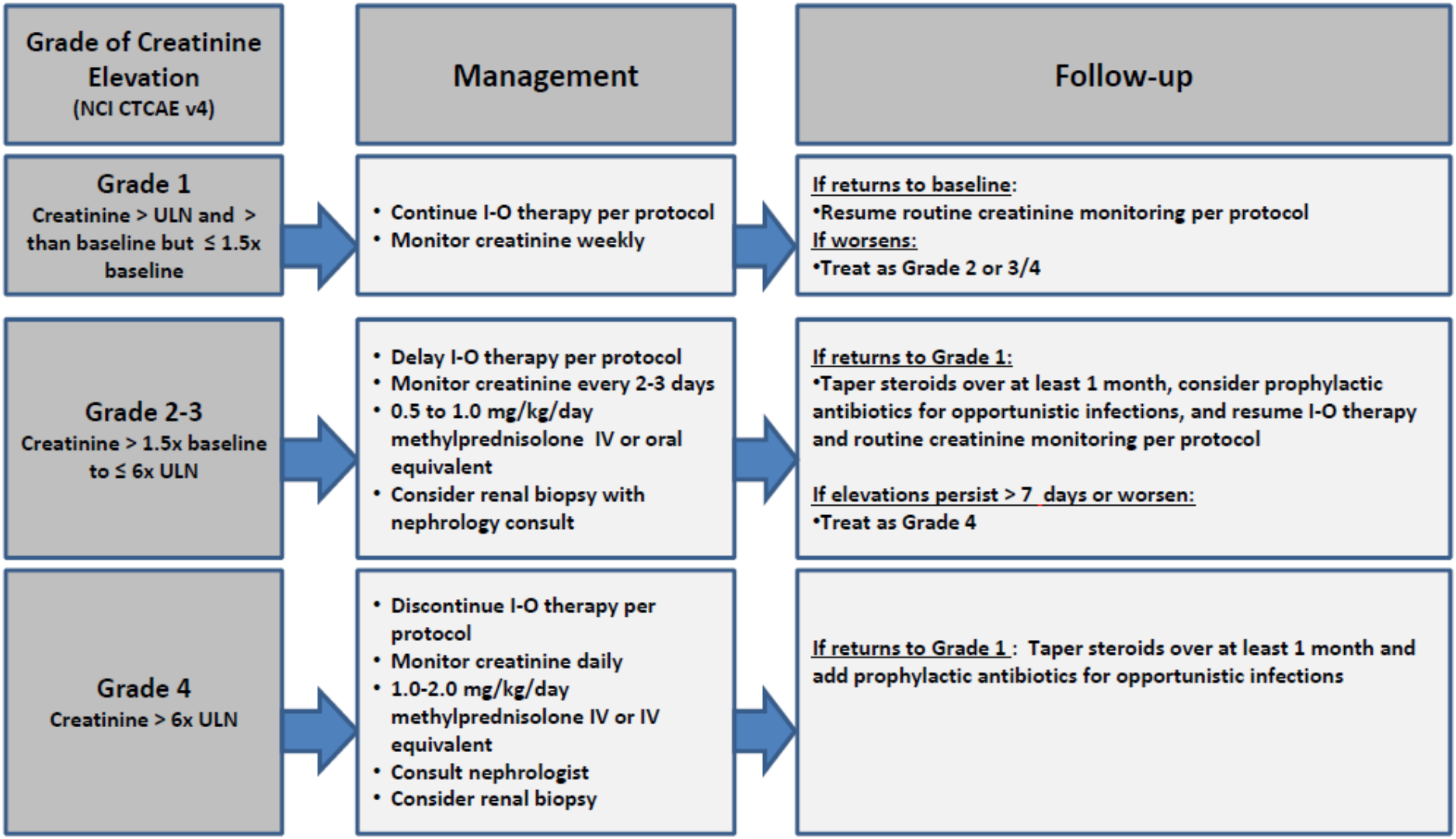


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

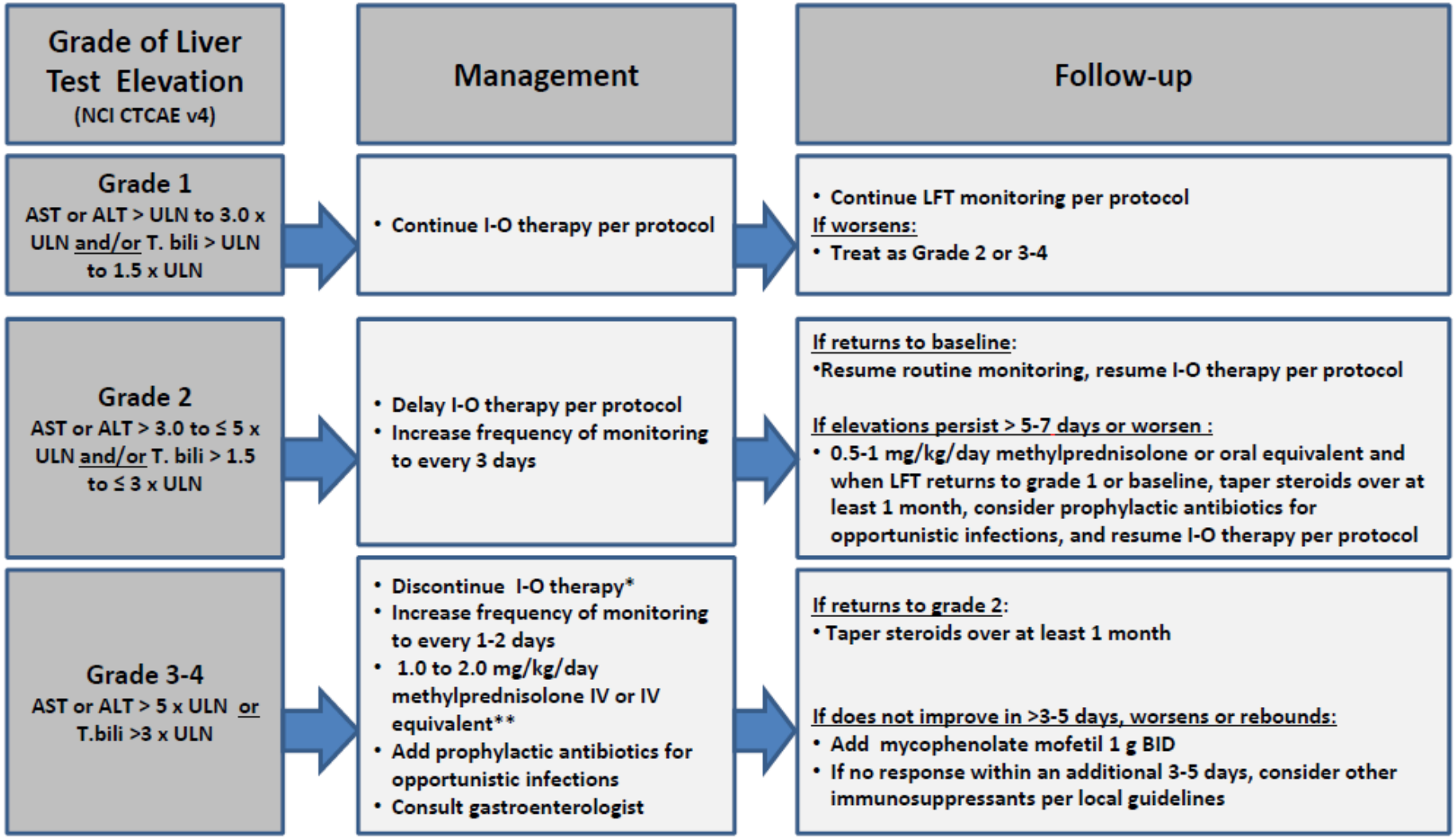
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms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

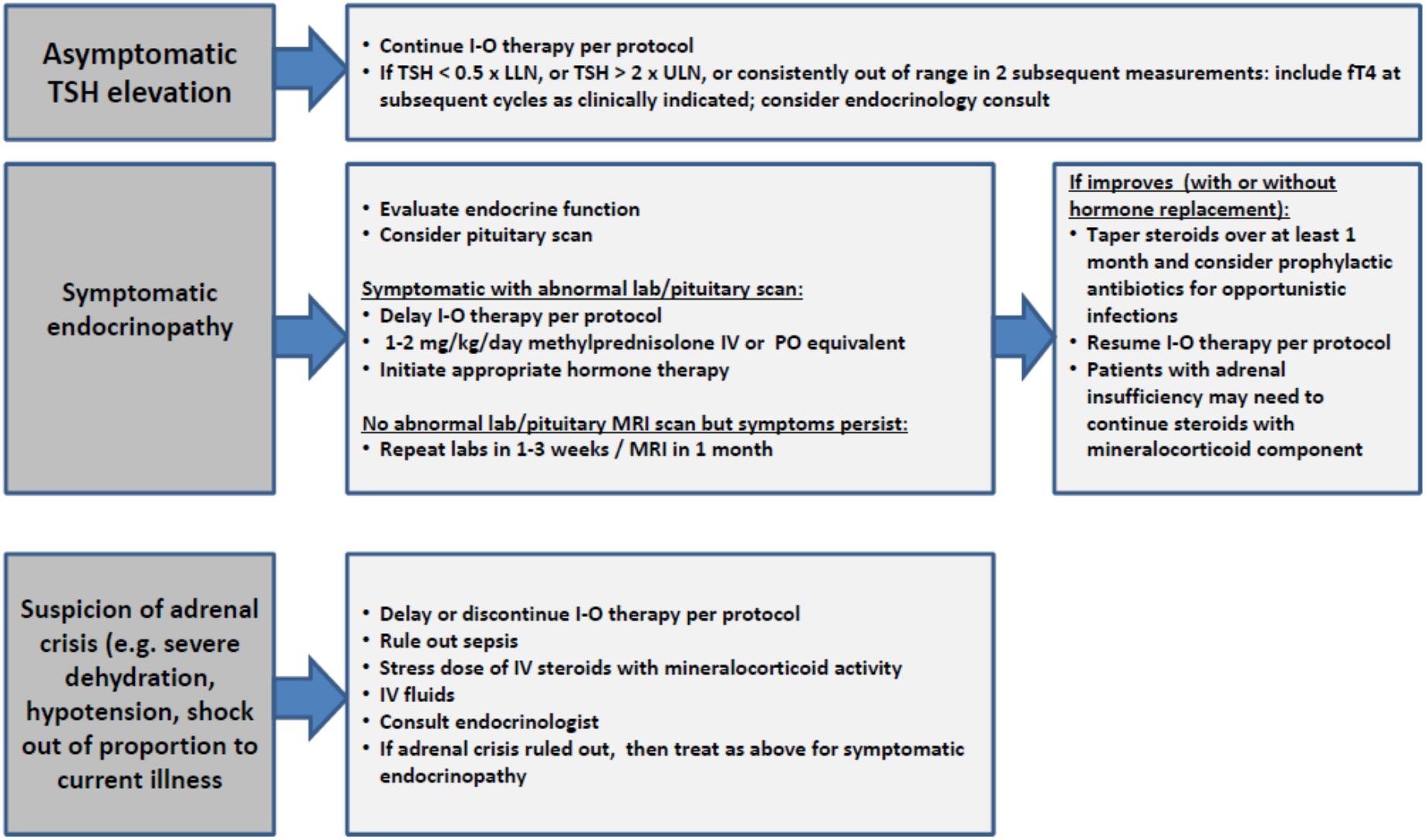
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**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.

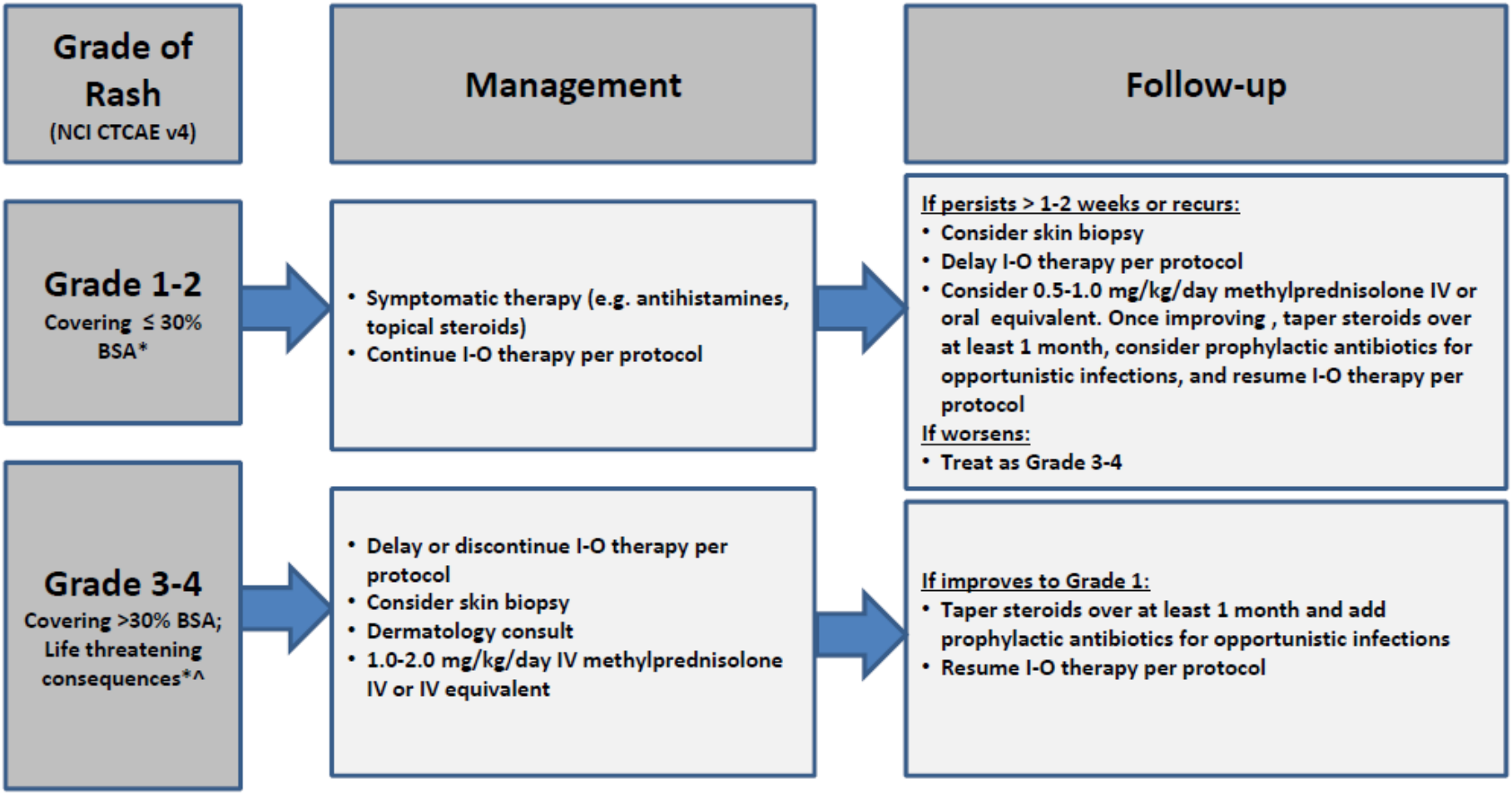


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Updated 05-Jul-2016