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PHASE II STUDY OF INDUCTION CHECKPOINT BLOCKADE FOR UNTREATED STAGE I-IIIA NON-SMALL CELL LUNG CANCERS AMENABLE FOR SURGICAL RESECTION

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1 BACKGROUND

Surgical resection remains the preferred treatment approach for patients with stage I, II, and selected stage III non-small cell lung cancers. Nonetheless, a substantial number of patients will recur after surgical resection alone. As such, the use of peri-operative cytotoxic therapy has been developed to improve outcomes in this setting.

Adjuvant chemotherapy. Cisplatin-based adjuvant chemotherapy has become the standard of care treatment following surgical resection of patients with lymph node positive non-small cell lung cancer, based on data from three randomized controlled studies (1-3). A meta- analysis including 4584 patients and 5 trials demonstrated a hazard ratio (HR) for death of 0.89 in favor of adjuvant chemotherapy compared to surgery alone (95% confidence interval [CI] 0.82-0.96, p=0.005), which translates to an absolute improvement in 5-year overall survival of 5.4% (4).

Neoadjuvant (induction) systemic therapy. Early randomized, single-institution, small scale studies evaluating the role of induction chemotherapy in patients with stage III NSCLC provided evidence for potential benefits from systemic therapy prior to surgical resection. Despite the small sample size, Roth et al., and Rosell et al. found statistically significant improvements in overall survival for patients assigned to receive induction treatment, compared to the control arm of surgery alone (5, 6). Following this experience, several multi-institutional, randomized, phase III studies were launched to evaluate the effects of induction chemotherapy in patients with stage I-III NSCLC (7-11). Collectively, these studies demonstrated that (1) induction treatment had activity in NSCLC and elicited objective responses in at least 40% of the patients; (2) there was no significant increase in peri- operative mortality; (3) induction chemotherapy did not seem to negatively impact disease resectability. Furthermore, a meta-analysis including seven induction randomized trials (988 patients), demonstrated a HR for death of 0.82 (95% CI 0.69-0.97, p=0.002) in favor of induction treatment, translating into an absolute improvement of overall survival at 5 years of 6% (12). Since these figures are very similar to the benefits seen in the adjuvant chemotherapy meta-analysis, one could argue that chemotherapy, either before or after surgery, are reasonable treatment options in patients that are candidate for peri-operative systemic therapy.

Potential advantages of neoadjuvant compared to adjuvant treatment include: (1) the ability to deliver treatment with higher dose intensity, due to better tolerability (10); (2) the ability to demonstrate sensitivity to treatment in vivo (since one can follow response to therapy by imaging studies, and assess pathologic response in the resected specimen) – the in vivo

assessment of treatment efficacy provides important prognostic information, since patients with a partial or complete radiographic response to treatment (13), and patients with lymph node pathologic downstaging after therapy have been shown to have improved survival (14-16); (3) the ability to study biomarker modulation in response to therapy, and correlate them with short- term (i.e., response rates), and long-term (i.e., disease-free or overall survival) efficacy outcomes, thus streamlining translational research.

Induction systemic therapy may be particularly important in the setting of immune checkpoint inhibitor use. One might postulate that, in contrast to the adjuvant setting (in which only micro-metastatic disease is present), the higher tumor burden present at the time of induction treatment may be necessary for abundant antigen release and presentation to the immune system, and consequently, development of a robust immune response. The possible superiority of induction immune therapy, as compared to adjuvant immune therapy, is currently being investigated in pre-clinical models at MD Anderson (Cascone et al, manuscript in preparation).

Nivolumab. Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD- L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Please refer to the Investigator's brochure for further information on nivolumab.

Ipilimumab. Ipilimumab is a fully human monoclonal IgG1κ 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 is a monoclonal antibody that 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 tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Please refer to the Investigator's brochure for further information on ipilimumab.

Nivolumab for NSCLC. The results of two phase III trials led to the FDA approval of nivolumab for patients with advanced squamous and non-squamous NSCLC who had disease recurrence after one prior platinum-based chemotherapy regimen. The CheckMate 017 was a

randomized, open-label, multinational, phase III trial comparing the efficacy and safety of nivolumab 3 mg/kg every 2 weeks versus docetaxel 75 mg/m2 every 3 weeks in patients with advanced, squamous NSCLC. The median OS was 9.2 months with nivolumab and 6.0 months with docetaxel, with 1-year OS rates of 42 and 24 %, respectively, and 18-month OS rates of 28 and 13% respectively. The HRs for OS favored nivolumab versus docetaxel across various pre-specified subgroups, apart from the 'rest-of-world' geographic region and patients aged ≥75 years. The confirmed ORR was significantly higher in nivolumab than in docetaxel recipients. A CR was seen in 1 % of nivolumab recipients and 0 % of docetaxel recipients and a PR occurred in 19 and 9 % of patients in the corresponding treatment groups. The median PFS was 3.5 months with nivolumab and 2.8 months with docetaxel (17). The CheckMate 057 was a randomized, open-label, international phase 3 study, in which patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy were randomized to receive nivolumab at a dose of 3 mg/kg every 2 weeks or docetaxel (75 mg/m2) every 3 weeks. In this trial, the median OS was 12.2 months among 292 patients in the nivolumab group and 9.4 months among 290 patients in the docetaxel group (hazard ratio for death, 0.73; P=0.002). At 1 year, the overall survival rate was 51% with nivolumab versus 39% with docetaxel. The RR was 19% with nivolumab versus 12% with docetaxel (18). The preliminary results of a small scale phase 2 study evaluating the safety and feasibility of neoadjuvant nivolumab for early stage NSCLC patients were recently published (19). Neoadjuvant nivolumab induced major pathologic response in 45% (9/20) of evaluable patients, which is markedly increased relative to the one noted following neoadjuvant chemotherapy (19%) (20). Furthermore, the authors showed a correlation between both pre-treatment tumor mutation and predicted neo-antigen loads with pathologic response. Immunohistochemical analysis of pre- and post-treatment tumors showed an influx of PD-$1^{+}CD8^{+}$ T cells into responding tumors. These results indicate that nivolumab is safe and neither delays surgery nor induces surgical complications when given preoperatively.

Combination of nivolumab and ipilimumab for NSCLC. CheckMate 012 compared several dosing schedules for combining nivolumab and ipilimumab for front-line use in treating advanced NSCLC to explore the safety and efficacy of dual checkpoint therapy in the metastatic setting. Initially, the combination with ipilimumab mirrored the dose and schedules used in metastatic melanoma (nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks or nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks). Response rates with these combinations were 13% and 20%, respectively. Grade 3/4 treatment-related adverse event rates were 58% and 44%, and 37% of patients discontinued this combination due to toxicity. Given the toxicities encountered in the initial experience of the combination of ipilimumab and nivolumab in metastatic NSCLC, modified dose schedules have been studied:

- Nivolumab at 1 mg/kg every 3 weeks × 4 plus ipilimumab at 1 mg/kg every 3 weeks

× 4 plus nivolumab at 3 mg/kg every 2 weeks (n = 31)

- Nivolumab at 1 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg every 6 weeks (n = 40)
- Nivolumab at 3 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg every 12 weeks (n = 38)
- Nivolumab at 3 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg every 6 weeks (n = 39).

Efficacy and safety results of the Checkmate 012 study were recently published by Hellmann et al. (21). The combination was well tolerated in all the cohorts. Only 11-13% of patients discontinued treatment due to adverse events. This compares favorably to what was seen with first-line nivolumab monotherapy (10%). Grade 3/4 treatment-related adverse events occurred in 33% to 37% of patients and were manageable. There were no treatment-related deaths. The study also demonstrated a high level of clinical activity characterized by deep and durable responses. Objective responses were confirmed in 43% in the overall population (≥50% PD-L1, ≥1% PD-L1, and <1% PD-L1), and ranged from 47% to 39% in the cohorts receiving nivolumab at 3 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg every 12 weeks or every 6 weeks, respectively. Median duration of response was not reached in any arm, regardless of PD-L1 expression, with median follow-up times of 12.8 months in the ipilimumab every 12 weeks cohort and 11.8 months in the ipilimumab every 6 weeks cohort (21).

Combination of nivolumab and platinum-based chemotherapy for NSCLC. The PD-1 inhibitor pembrolizumab has shown superior efficacy as monotherapy in previously untreated patients with advanced NSCLC and a PD-L1 tumor proportion score ≥50% compared with standard platinum-based chemotherapy, with fewer toxicities (22). Based on this results, the investigators of the Keynote-021 phase II study assessed the efficacy of pembrolizumab added to platinum-doublet chemotherapy as first line therapy for advanced non-squamous NSCLC patients (23). The objective response rate was 55% in the pembrolizumab plus chemotherapy group compared with 29% in the chemotherapy alone group (p=0.0016) with an overall tolerable toxicity profile. More recently, the IMpower150 phase 3 trial is evaluating the addition of the PD-L1 inhibitor atezolizumab (atezo) to carboplatin (C) + paclitaxel (P) ± bevacizumab (bev) in chemo-naive patients with metastatic non-squamous NSCLC. The initial results of this trial has been recently presented by Reck et al at the ESMO Immuno-Oncology Congress 2017 (24) . Median PFS in atezo + bev 15 mg/kg + C + P (Arm B) vs. bev + C + P (Arm C) was 8.3 months vs 6.8 months and 11.3 months vs 6.8 months in the ITT-wild type (WT) and in WT pts with expression of a tumor T-effector gene signature,

respectively. PFS benefit was seen regardless of PD-L1 IHC status, including PD-L1–negative pts. Arm B had a comparable safety profile to Arm C; treatment-related serious adverse events were 25% vs 19%, respectively. This is the first phase III trial to show a statistically significant and clinically meaningful PFS benefit with atezo + bev + chemo as compared with bev + chemo in previously untreated pts with non-squamous metastatic NSCLC.

The phase III trial, KEYNOTE-189, was a randomized, double blind, placebo controlled, study investigating pembrolizumab in combination with pemetrexed and cisplatin or carboplatin compared with pemetrexed and cisplatin or carboplatin alone in previously untreated patients with wild type (WT) advanced or metastatic nonsquamous NSCLC, regardless of PD-L1 expression (NCT02578680). The results of this phase 3 trial have been recently reported and demonstrated that in patients with previously untreated metastatic nonsquamous NSCLC without *EGFR* or *ALK* mutations, the addition of pembrolizumab to standard pemetrexed plus platinum-based chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone. After a median follow-up of 10.5 months, the 12-month OS rate was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group vs. 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group (HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001). Median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001) (25). Another phase III trial, CheckMate 227, compared nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum-based chemotherapy versus platinum-based chemotherapy in patients with chemotherapy-naïve stage IV recurrent NSCLC (NCT02477826). Results have been recently reported and demonstrated that PFS among patients with a high tumor mutational burden was significantly longer with nivolumab plus ipilimumab than with chemotherapy. The 1-year PFS rate was 42.6% with nivolumab plus ipilimumab vs. 13.2% with chemotherapy, and the median PFS was 7.2 months (95% confidence interval [CI], 5.5 to 13.2) vs. 5.5 months (95% CI, 4.4 to 5.8) (HR for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; P<0.001). The ORR was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy (26).
Collectively, these results and the ongoing studies support investigation of checkpoint inhibitors with or without platinum-based chemotherapy in the pre- operative setting.

Combination of nivolumab plus ipilimumab (dual ICI) and platinum-based chemotherapy plus dual ICI for advanced/metastatic NSCLC. CheckMate 568 was an open-label phase II trial that evaluated the efficacy and safety of nivolumab plus low-dose ipilimumab as first-line treatment of advanced/metastatic NSCLC patients (27). Two hundred eighty-eight patients with previously untreated, recurrent stage IIIB/IV NSCLC received nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. The primary end point was

objective response rate (ORR) in patients with 1% or more and less than 1% tumor PD-L1 expression. Efficacy on the basis of TMB (FoundationOne CDx assay) was a secondary end point. ORR was 30% overall and 41% and 15% in patients with 1% or greater and less than 1% tumor PD-L1 expression, respectively. ORR increased with higher TMB, plateauing at 10 or more mutations/megabase (mut/Mb). Grade 3 to 4 treatment-related adverse events occurred in 29% of patients. Nivolumab plus low-dose ipilimumab was effective and tolerable as a first-line treatment of advanced/metastatic NSCLC. In the second phase of this study, 36 previously untreated stage IV/recurrent stage IIIb NSCLC patients without the presence of a known tumor genomic driver (PD-L1 TPS all comers), have been treated with 2 cycles of nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks plus platinum doublet chemotherapy followed by nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity for a maximum of 2 years. With a median follow up time of 15.5 months, 1 case of dose limiting toxicity (DLT) was observed with one patient experiencing a Grade 3 ALT/AST elevation that resulted in ipilimumab discontinuation after cycle 1. Patient continued treatment with nivolumab plus platinum doublet chemotherapy with a 50% tumor size reduction. Overall 92% of treated patients experienced treatment-related AEs of any grade (Grade 3-4 61%, Grade 5 0), and in 19% of patients treatment had to be discontinued to drug-related toxicities, which included 2 cases of pneumonitis, 2 colitis, 2 cases of encephalopathy, 1 case of acute kidney injury and 1 adrenal insufficiency. Most patients received the pre-planned 2 cycles of chemo (1/36 stopped therapy due to vomiting and febrile neutropenia). In summary, the initial safety profile of the first 36 patients treated with the combination of nivolumab, low dose ipilimumab and 2 cycles of platinum doublet chemotherapy was manageable and consistent with the known profile of combination (unpublished data). No new safety issues were identified and lower frequency of potential chemotherapy- related toxicities was noted as compared to historical standard of care controls with 4 cycles of chemotherapy platinum doublet +/- pembrolizumab in the first line setting for metastatic NSCLC patients, suggesting that the combination of nicolumab, low dose ipilimumab and platinum doublet chemotherapy may be a safe and more potent therapeutic strategy in the neoadjuvant setting for resectable NSCLC patients.

Major pathologic response as a marker of induction chemotherapy efficacy. Several small studies have suggested that the degree of tumor regression after induction therapy, as determined by histopathologic findings in the resected tumor, may be an objective criterion of chemotherapy response and may correlate with long-term treatment outcomes (28-31). This issue was comprehensively evaluated recently by Pataer et al. in a retrospective study with 192 patients treated with induction chemotherapy and 166 patients treated with surgery upfront at M. D. Anderson (20).Using a score system that quantifies the percentage of viable tumor cells in at least 1 section per cm of tumor greatest diameter (5-30 slides examined for each case), the authors demonstrated that in patients that received induction treatment, there is a statistically

significant correlation between higher percentage of viable cells and shorter disease-free and overall survival. This correlation was not evident in patients treated with surgery upfront. In this cohort, 89% of the neoadjuvant treated patients received a platinum and a taxane-based regimen, and a pathologic response (defined as ≤ 10% viable tumor cells) occurred in 19% of the patients. The 5-year recurrence-free survival for patients with and without a pathologic response were 78% and 35%, respectively ($p < 0.001$). The 5-year overall survival for patients with and without a pathologic response were 85% and 40%, respectively ($p < 0.0001$). Taken together, these results support the use of major pathologic response as a surrogate endpoint for recurrence-free and overall survival in patients with NSCLC treated with neoadjuvant chemotherapy.

Neoadjuvant Immune checkpoint blockade in resectable NSCLC
Recently published results of a small, pilot study evaluating the safety and feasibility of neoadjuvant nivolumab as monotherapy for a limited number of patients with resectable NSCLC has demonstrated that nivolumab is safe, does not delay surgery, and induces a major pathological response in 9 of 20 resected tumors (45%) (19). Translational analyses revealed a significant correlation between the pathological response and the pretreatment tumor mutational burden, and the number of T-cell clones that were found in both the tumor and peripheral blood expanded significantly after neoadjuvant nivolumab therapy in 8/9 patients evaluated. These remarkable results highlights the need to test additional immunotherapy-based combination in the neoadjuvant setting to discover efficacy signal of compounds to be tested in larger trials.

TCD8$^+$ TILs as a prognostic marker. Several studies have demonstrated that TCD8$^+$ TILs are associated with improved outcomes in resected NSCLCs (32-34). PD-1 and/or CTLA4 blockade are expected to recruit antigen-specific TCD8$^+$ cells to the tumor microenvironment, and therefore contribute to an enhanced immune response. As such, automated quantification of TCD8$^+$ cells in resected specimens following induction immunotherapy may provide evidence for its role as a surrogate marker of efficacy of these drugs, and is included as a secondary endpoint in this study. Additionally, phenotypic characterization of the immune infiltrate (such as evaluation of exhausted T cells) may also be important to evaluate potential differences in outcomes to single agent versus combined immune checkpoint blockade (35).

2 STUDY OBJECTIVES

2.1 Hypotheses

The primary hypothesis to be tested in this study is that, in patients with stage I-IIIA NSCLC amenable for surgical resection, induction immunotherapy with nivolumab alone and/or nivolumab plus ipilimumab and/or single or combined immunotherapy plus platinum-based chemotherapy will produce major pathologic responses of at least 40%, a target response that is superior to the one observed following induction platinum-based chemotherapy alone, as compared to the MD Anderson historical controls.

The secondary hypothesis to be tested in this study is that immunotherapy with nivolumab and/or nivolumab plus ipilimumab and/or single or combined immunotherapy plus platinum-based chemotherapy will induce immune responses (as assessed by CD8+ TILs), tumor shrinkage (as assessed by CT), and improve recurrence-free survival (RFS) and overall survival (OS) in a subset of patients; analysis of correlative studies in these patients will assist in developing biomarkers predictive of response to immunotherapeutic agents in NSCLC and will assist in determining immune modulation by nivolumab alone and/or nivolumab plus ipilimumab and/or single or combined immunotherapy plus platinum-based chemotherapy .

2.2 Study Endpoints

2.2.1 Primary endpoint

- Major pathologic response rate in patients treated with induction nivolumab, nivolumab plus ipilimumab, and single or combined immunotherapy plus platinum-based chemotherapy.

Major pathologic response is defined as ≤ 10% viable tumor cells in the resected specimen using the methods described by Pataer et al (20). Briefly, at least 1 section per cm of tumor greatest diameter is evaluated, with a minimum of 5 slides. The percentage of residual tumor is determined by comparing the estimated cross sectional area of the viable tumor foci to estimated cross sectional areas of necrosis, fibrosis and inflammation on each slide. The results for all slides are averaged together to determine a mean value of viable tumor

cells for each patient.

2.2.2 Secondary endpoints

- Toxicity (assessed by the NCI CTCAE version 4)

- Peri-operative morbidity and mortality

- CD8+ TILs in resected tumor tissues of patients treated with nivolumab alone and nivolumab plus ipilimumab and single or combined immunotherapy plus platinum-based chemotherapy.

- Quantification of CD8+ TILs will be assessed by counting the cells positive for staining with an anti-CD8 antibody by immunohistochemistry in five random square areas (1 mm^2 each) in both intratumoral and peritumoral compartments using the automated Aperio system.

- Response rates to induction treatment (by RECIST version 1.1) (36)

- Recurrence-free survival

- Overall survival

- To correlate major pathologic response with recurrence-free and overall survival

- Complete resection (R0) rate

- Pathologic complete response (pCR) in resected tumor specimens

- To correlate response assessed by imaging studies with outcomes (both major pathologic response to treatment and long-term recurrence-free survival)

- To correlate blood, tissue, and stool-based biomarkers with efficacy and toxicity

2.2.3 Exploratory endpoints

An important aspect of this trial is to identify novel prognostic and predictive markers present at diagnosis, and to determine modulation of markers by induction immunotherapy and/or immunotherapy plus platinum-based chemotherapy in order to inform future translational studies. As such, blood, stools and tumor tissue will be collected throughout the study period. The markers to be assessed in these specimens (likely with the use of high throughput technology) will be determined according to the best scientific knowledge and technology available at the time of batch analysis. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials. Candidate markers to be evaluated include (but are not restricted to):

- PD-L1 expression in tumor tissue

- Multi-region next generation DNA and/or RNA sequencing in tumor tissue (including whole exome and/or whole genome sequencing) and in blood/normal tissue, so that tumor heterogeneity and mutational load can be correlated with efficacy of immunotherapy and/or other correlative markers

- Immunophenotyping or characterization of the immune cell subsets in tumor tissue, including markers of T cell exhaustion (CD3, PD-1, CD4, CD8, CTLA-4, CD45), T cell activation (CD3, CD28, CD44, CD8, CD62L, CD45), T regulatory cells (CD3, FOXP3, CD8, CD4, CD25, CD45), T cell function (CD3, IFN-gamma, CD4, CD8, IL10, CD45), antigen presenting cells (CD11B, CD11C, GR-1, CD86, PD-L1, CD45), as well as CD20, Ki67, granzyme B, IFN-γ, TGF-beta, GATA-3, RORgt, BCL2 (thus allowing for estimation of T cell activation, and Th1/Th2/Th17 bias), as well as CD68 and other markers relevant to immune profiling.

- Expression of immunoregulatory and co-stimulatory markers in TILs by flow cytometry, including, but not limited to, PD1, CTLA4, LAG3, 41BB, and TCR zeta chain

- RNA and protein expression in tumor and adjacent normal tissue, including assessment of immune/inflammatory pathways

- Immunophenotyping or characterization of the immune cell subsets in the periphery,

including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types

- Single cell genomics in tumor and adjacent normal tissue

- Serum soluble factors, including IFN-gamma and interferon inducible factors (such as CXCL9 and CXCL10), PD-L1, PD-1, anti-tumor antibodies, microRNAs (such as miR-513, and miR19b), IL-12, TNFα, IL-10, TGF-β, VEGF, IL-6, IL-8, IL-17, IL-18, C-reactive protein and, as well as other cytokines, chemokines, inflammatory factors and immune mediators

- T cell receptor repertoire sequencing in tumor tissue and the periphery

- Next generation sequencing of cell-free circulating DNA

- Immunopeptidome analysis

- Enteric microbiome analysis

- CT imaging analysis

2.2.4 Additional assessments

In addition to the endpoints described above, post-treatment TILs will also be isolated, expanded and evaluated for anti-tumor activity *in vitro*. TILs may also be stored for future re-infusion into patients that develop disease recurrence as part of a separate clinical trial. We hypothesize that the efficiency of TIL isolation and efficacy of adoptive T-cell therapy will be improved when cells are collected post exposure to checkpoint inhibitors, thus providing further rationale for developing induction immunotherapy strategies in resectable NSCLCs.

We may also establish cell cultures and patient-derived xenografts in rodents from tissues obtained under this protocol for future pre-clinical studies. Procedures for establishing and maintaining xenografts will be contemplated in a separate animal protocol.

3 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives, and In compliance with the protocol.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

4 ELIGIBILITY CRITERIA

All eligibility criteria must be met prior to initiating treatment.

4.1 Inclusion Criteria

1. Age $\geq$ 18 years

2. Histologically or cytologically confirmed previously untreated non-small cell lung cancer. If a diagnostic biopsy is available, a pre-treatment biopsy is not required. Patients with a suspected lung cancer are eligible, but pathology must be confirmed prior to initiating treatment on study. Neuroendocrine carcinomas are not eligible. Carcinomas with neuroendocrine differentiation are eligible.

3. Patients with stage IA or stage IB < 4 cm (according to AJCC 7th edition) are eligible for randomization into arms A and B only. Patients with stage IB $\geq$ 4cm, IIA, IIB, or IIIA disease (according to AJCC 7th edition) are eligible for randomization into arms A and B, and for enrollment into arms C and D.

4. Patients with stage IIIA must not have more than one mediastinal lymph node station involved by tumor.
5. All patients must have lymph node evaluation of contralateral stations 2 and/or 4 to exclude N3 disease (see section 9.1.5).

6. The patient must be a suitable candidate for surgery, in the opinion of the treating physician.

7. Signed and dated written informed consent must be provided by the patient prior to admission to the study in accordance with ICH-GCP guidelines and to the local legislation

8. ECOG performance status score 0-1

9. Patients must have organ and marrow function as defined below:

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC) Hemoglobin Platelets	$\geq 1.5 \times 10^9$/L ≥ 8.0 g/dL $\geq 100 \times 10^9$/L
Hepatic	

Total bilirubin AST and ALT	≤ 1.5 X ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) ≤3 X ULN
Renal	
Creatinine OR Calculated creatinine clearance[1] OR 24-hour urine creatinine clearance	≤1.5 X ULN ≥ 50 mL/min ≥ 50 mL/min

[1] *Cockcroft-Gault formula for creatinine clearance calculation:*

Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

4.2 Exclusion Criteria

1. Prior systemic therapy or radiation therapy for treatment of the current lung cancer

2. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) or investigational anti-cancer drug
3. Pregnant or lactating female

- Women of childbearing potential (WOCB) must have a negative serum or urine
- pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of nivolumab
- Women of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes

4. Unwillingness or inability to follow the procedures required in the protocol
5. Patients with pre-existing sensorineural hearing impairment/loss or newly diagnosed as documented by an audiology assessment performed prior to study enrollment may not be eligible for cisplatin and may be dispositioned to carboplatin, as determined by the treating physician.

6. Patients with a history of severe hypersensitivity reaction to Taxotere® and or polysorbate 80 must be excluded
7. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results. Prior malignancy active within the previous 2 years. Patients with locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast with local control measures (surgery, radiation) are eligible.
8. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
9. Subjects with a condition requiring systemic treatment with either corticosteroids (>

10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

- Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

10. Prior treatment with an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody

11. Known positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid indicating acute or chronic infection

12. Known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome

13. History of severe hypersensitivity reaction to any monoclonal antibody and/or to study drug components

14. Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study.

15. Patients who are sexually active, with preserved reproductive capacity, and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females, condoms for participating males) during and after the trial as detailed below

- WOCBP should use an adequate method to avoid pregnancy for 23 weeks after the last dose of investigational drug(s).
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year.
- Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.
- Women who are not of childbearing potential as well as azoospermic men do not require contraception

16. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule.

5 STUDY DESIGN AND PLAN

Modular design of neoadjuvant signal-finding study platform

Given the promising activity and safety demonstrated by neoadjuvant nivolumab, several immunotherapy-based regimens are now being tested in the neoadjuvant setting in phase 2 studies using the MPR as primary endpoint of efficacy. It follows that the best approach to expedite the evaluation of novel and active therapeutic strategies that merit further investigation in larger randomized trials, would be a modular platform clinical trial of single arm, signal-finding and efficacy-testing studies. Based on this design, upon completion of a proposed single arm study, a follow-on evaluation could result in a randomized comparison, if a signal of activity is observed, or the launch of another single arm study evaluating a new immunotherapy combination, if the proposed study fails to demonstrate a signal of activity.

Study Plan

This is an open label, phase 2 multi-arm study with modular design of nivolumab, nivolumab plus ipilimumab, single or combined immunotherapy plus platinum-based chemotherapy induction treatment in patients with resectable NSCLC, with the primary objective to determine the MPR in each arm, and compare it not between arms, but to the benchmark from historical controls of neoadjuvant chemotherapy. After confirmation of eligibility criteria, patients will be stratified by stage (I vs. II vs. III) and randomized to Arm A or Arm B using a minimization technique. Upon completion of enrollment in these two arms, eligible patients will be enrolled to Arm C or D.

Arm A — nivolumab single agent

Arm B — nivolumab plus ipilimumab

Arm C — nivolumab plus platinum-based chemotherapy

Arm D — nivolumab plus ipilimumab plus platinum-based chemotherapy

For patients accrued to Arms A and B, randomization will be performed via a centralized, web-based randomization system – the Clinical Trial Conduct (CTC) application in the Department of Biostatistics. Patients who are randomized will be assigned to a treatment arm and given a unique patient number by the centralized, web-based system.

6 TREATMENT

6.1 Induction Treatment

Patients will receive induction treatment according to the randomization arm, as follows:

Arm A:

- Nivolumab 3 mg/kg intravenously on days 1, 15, and 29

Arm B:

- Ipilimumab 1 mg/kg intravenously on day 1, and

- Nivolumab 3 mg/kg intravenously on days 1, 15, and 29

Upon completion of randomization to Arms A and B, patients will be accrued to Arm C:

- Nivolumab 360 mg IV every 3 weeks (D1, D22, D43) plus Cisplatin and Docetaxel IV administered every 3 weeks (D1, D22, D43), up to a maximum of 3 cycles for squamous histology NSCLCs, or Nivolumab 360 mg IV every 3 weeks (D1, D22, D43) plus Cisplatin and Pemetrexed IV administered every 3 weeks (D1, D22, D43), up to a maximum of 3 cycles for non-squamous histology NSCLCs. For carcinomas with neuroendocrine features and/or differentiation either regimen with Cisplatin and Docetaxel plus Nivolumab or Ciplatin and Pemetrexed plus Nivolumab may be used based on treating physician's preference.

Upon completion of enrollment to Arm C, patients will be accrued to Arm D:

- Ipilimumab 1 mg/kg intravenously on day 1 only plus Nivolumab 360 mg IV every 3 weeks (D1, D22, D43) plus Cisplatin (or Carboplatin) and Docetaxel IV administered every 3 weeks (D1, D22, D43), up to a maximum of 3 cycles for squamous histology NSCLCs, or Ipilimumab 1 mg/kg intravenously on day 1 only plus Nivolumab 360 mg IV every 3 weeks (D1, D22, D43) plus Cisplatin (or Carboplatin) and Pemetrexed IV administered every 3 weeks (D1, D22, D43), up to a maximum of 3 cycles for non-squamous histology NSCLCs. For carcinomas with neuroendocrine features and/or differentiation Cisplatin (or Carboplatin) and Docetaxel or Cisplatin (or Carboplatin) and Pemetrexed regimens plus Ipilimumab and Nivolumab may be used based on the treating physician's preference.

6.2 Surgery

Surgery will be performed after completion of induction therapy. It is strongly recommended that 3 doses of nivolumab (arms A and B) or 3 cycles of platinum-based chemotherapy plus nivolumab (arm C), or 3 cycles of platinum-based chemotherapy plus ipilimumab and nivolumab (arm D) are administered prior to surgery. However, less than 3 doses of nivolumab or 3 cycles of platinum-based chemotherapy plus nivolumab, or 3 cycles of platinum-based chemotherapy plus pilimumab and nivolumab will be allowed in case of excessive toxicities or other reasons identified by the treating physician that may lead to an unfavorable benefit/risk ratio of proceeding with therapy as planned per protocol, after discussing the case with the principal investigator.

There must be at least a 21-day nivolumab-free or platinum-based chemotherapy plus nivolumab-free interval before surgery (i.e., surgery will only be performed at least 21 days after the last dose of nivolumab or platinum-based chemotherapy plus nivolumab, unless there is a strong clinical indication to perform surgery sooner, in the opinion of the treating physician). It is strongly recommended that surgery be performed within 3 to 6 weeks after the last dose of nivolumab or nivolumab plus platinum-based chemotherapy.

The operative approach (thoracoscopy versus thoracotomy) and the extent of surgical resection will be based on the treating surgeon's judgment and may include wedge resection, segmentectomy, lobectomy, or pneumonectomy with mediastinal lymph node dissection of nodal stations 4, 7, 8, 9,10, 11-14 for right sided resections, and nodal stations 5, 6, 7, 8, 9, 10, 11-14 for left sided resection.

6.3 Post-operative (Adjuvant) Systemic Therapy

Since the primary efficacy endpoint of this study is major pathologic response (which will be assessed at the time of surgery), mandatory use or mandatory prohibition of post-operative (adjuvant) systemic therapy will not be defined by this protocol. Patients may receive adjuvant systemic therapy at the discretion of the treating physician. In general, if patients have completed 3 cycles of induction platinum-based chemotherapy, no adjuvant systemic therapy is recommended. For patients who did not receive induction platinum-based chemotherapy, and with stage IB (with tumor size 4 cm or greater), II, and III, at least 3 cycles of adjuvant cisplatin- based chemotherapy are recommended. In case adjuvant systemic therapy is used, this information will be captured by retrospective chart review and may be used for interpretation of analysis of long-term treatment outcomes.

6.4 Post-operative (Adjuvant) Radiation Therapy

Since the primary efficacy endpoints of this study is major pathologic response (which will be assessed at the time of surgery), mandatory use or mandatory prohibition of post-operative (adjuvant) radiation therapy will not be defined by this protocol. Post-operative radiation therapy will be delivered according to institutional guidelines and the treating physician's best judgement, preferably within 6 weeks of surgical resection or completion of adjuvant systemic therapy (whichever is longer). While radiation therapy is not formally required per protocol, it is strongly suggested that the following principles of radiation therapy be followed:

- Consider post-operative radiation therapy in patients with pathologic confirmation of mediastinal lymph node involvement by cancer either before or after induction treatment.

- Consider post-operative radiation therapy in patients with positive margins at surgical resection.

- When recommended, deliver either photon- or proton-based external beam radiation therapy between 50-66 Gy depending on the completeness of tumor resection. Typically 50 Gy in 25 fractions is given for R0 resection, 60 Gy in 30 fractions for R1, and 66 Gy in 33 fractions for R2 resection. The final dose will be left up to the treating radiation oncologist.

In case adjuvant radiation therapy is used, this information will be captured by retrospective chart review and may be used for interpretation of analysis of long-term treatment outcomes.

7 PRODUCT INFORMATION

7.1 Drug Ordering and Accountability

Only product supplied and designated for this protocol should be used for this study.

7.1.1 Nivolumab and Ipilimumab (Immune-Oncology [I-O] Agents)

BMS will supply study drugs nivolumab and ipilimumab used for this investigational study by ordering through a completed Drug Request Form provided by BMS for this specific trial.

- Please see Appendix 1 for information on provisions for ordering study drug from BMS. The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity)

- If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately. If commercial investigational product is used, it should be stored in accordance with the appropriate local labeling

- If the study drug(s) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures

7.1.2 Other agent(s)

Commercially available pemetrexed, cisplatin, carboplatin and docetaxel will be supplied by the study center (or according to local regulations). Pemetrexed, cisplatin, carboplatin and docetaxel should be stored as directed in the product package insert (or equivalent documentation). Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements.

7.2 Product Description and Dosage Form

7.2.1 Nivolumab and ipilimumab (I-O Agents)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8 C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

[a]Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer to the BMS- 936558 (nivolumab) and Ipilimumab Investigator Brochure section for "Recommended Storage and Use Conditions"

7.2.2 Other agent(s)

Pemetrexed
Commercially available pemetrexed will be supplied by the study center (or according to local regulations).

Cisplatin
Commercially available cisplatin will be supplied by the study center (or according to local regulations).

Carboplatin
Commercially available carboplatin will be supplied by the study center (or according to local regulations).

Docetaxel
Commercially available docetaxel will be supplied by the study center (or according to local regulations).

7.3 Handling and Dispensing

7.3.1 Nivolumab and Ipilimumab (I-O Agents)

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Please refer to the current version of the Investigator Brochure for additional information on storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

7.3.2 Other agent(s)

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Cisplatin

Cisplatin will be reconstituted as directed in the product package insert (or equivalent documentation).

Carboplatin

Carboplatin will be reconstituted as directed in the product package insert (or equivalent documentation).

Pemetrexed

Pemetrexed will be reconstituted as directed in the product package insert (or equivalent documentation).

Docetaxel

Docetaxel will be reconstituted as directed in the product package insert (or equivalent documentation).

7.4 Destruction

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed.

- 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, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for BMS to review throughout the clinical trial period as per the study agreement.

If conditions for destruction cannot be met, please contact BMS.

It is the Investigator's responsibility to arrange for disposal of all empty containers, 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.

7.5 Dose Administration

7.5.1 Nivolumab and ipilimumab (I-O Agents)

For preparation and administration details, please refer to the Investigator Brochure**.** When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion

BMS-936558 (nivolumab) is to be administered as a 60 minute IV infusion. Ipilimumab should be administered as a 90 minute infusion following.

Ipilimumab and nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

The dosing calculations should be based on the actual body weight. If the subject's 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 down per institutional standard.

Patients may be dosed no less than 9 days from the previous dose of drug; and dosed up to 7 days after the scheduled date if necessary.

7.5.2 Other agent(s)

Body surface area (BSA) for chemotherapy dose calculation will be determined according the following formula:
BSA (m^2) = (height (cm) x weight (kg)/3600)^{½}
or BSA (m^2) = square root of (height (cm) x weight (kg)/3600)

$$BSA(m^2) = \sqrt{\frac{HEIGHT(cm) x WEIGHT(kg)}{3600}}$$

The actual body weight will be used for BSA calculation, but the investigators will consider using adjusted or ideal body weight if the BSA exceeds 2.0 m2. BSA should be recalculated prior to the start of every cycle of therapy.

Agent(s)	Starting Dose	Route	Schedule
Docetaxel	75 mg/m^2	IV	Day 1 q 21 days + 7 days/-3 days [a]
Cisplatin	75 mg/m^2	IV	Day 1 q 21 days + 7 days/-3 days [a]
Or Carboplatin	AUC 5 or 6	IV	Day 1 q 21 days + 7 days/-3 days [a]
[a] For a maximum of 3 cycles.			

Agent(s)	Starting Dose	Route	Schedule
Pemetrexed	500 mg/m^2	IV	Day 1 q 21 days + 7 days/-3 days [a]
Cisplatin	75 mg/m^2	IV	Day 1 q 21 days + 7 days/-3 days [a]
Or Carboplatin	AUC 5 or 6	IV	Day 1 q 21 days + 7 days/-3 days [a]
[a] For a maximum of 3 cycles.			

Docetaxel and cisplatin or carboplatin, or pemetrexed and cisplatin or carboplatin will be prepared and administered according to local practice and in accordance with the most recent Package Inserts/Data Sheets.

For participants who are unable to tolerate cisplatin, the reasons for intolerability should be documented and the investigator can use a carboplatin-based regimen.

7.5.3 General Concomitant Medication and Supportive Care Guidelines

Prophylactic G-CSF support is strongly recommended and should be administered at least 24 hours after infusion of chemotherapy, beginning at cycle 1 and continued for the duration of treatment with chemotherapy. Treating physicians may consider discontinuing G-CSF administration at cycles ≥ 2 provided that the patient did not have febrile neutropenia or grade4 neutropenia lasting ≥ 7 days on previous cycles, and provided that the patient is experiencing adverse events associated with G-CSF administration.

Management of nausea and vomiting during platinum-based chemotherapy (including cisplatin and/or docetaxel and/or pemetrexed and/or carboplatin dose reductions) with the use of prophylactic anti-emetics will be implemented at the discretion of the treating physician.

To reduce the severity of fluid retention and hypersensitivity reactions related to docetaxel, all patients will be considered for pre-medication with corticosteroids, such as oral dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration. Considerations for modification of the corticosteroid regimen (including schedule and dose reductions) should be made in patients receiving the prophylactic anti-emetics fosaprepitant or aprepitant.

In order to reduce treatment-related hematologic and GI toxicities related to pemetrexed, patients will also be required to take folic acid, 350-1000 ug orally daily beginning approximately 5 days before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. In addition, Vitamin B12, 1000 ug, will be injected intramuscularly on day 1 of the first dose of pemetrexed and will be repeated approximately every 9 weeks until discontinuation of chemotherapy.

8 DOSE MODIFICATIONS AND TOXICITY MANAGEMENT

The toxicity management outlined herein is considered a general guideline. The investigator should use his or her best judgment when determining treatment interruptions. For example, some grade 2 non-hematologic toxicities may require treatment delays, and some grade 3 or 4 organ toxicities (e.g., hepatic, renal, cardiac, central nervous system) may require a permanent treatment discontinuation.

8.1 Management Algorithms for Immuno-oncology (I-O) Agents

There will be no dose modifications permitted. Dose reductions or dose escalations are not permitted.

Immuno-oncology (IO) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological.

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The algorithms recommended for utilization are attached as Appendix 2.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressant to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

- Early consultation with an infectious disease specialist should be considered.

  Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the Investigator's Brochure.

8.1.1 Dose delay criteria for I-O agents

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab or both). All study drugs must be delayed until treatment can resume.

Nivolumab administration should be delayed for the following:

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

- Grade 2 drug-related fatigue or laboratory abnormalities that 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. It is recommended to consult with the principle investigator for Grade 3 amylase or lipase abnormalities.

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

- If a subject 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 which, in the judgment of the investigator, warrants delaying the dose of study medication.

8.1.2 Criteria to resume treatment with I-O agents

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

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

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- Subjects 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

- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.4) should have treatment permanently discontinued

- Drug-related pulmonary toxicity, diarrhea, or colitis, 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 subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time points will be delayed until dosing resumes.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

8.1.3 Treatment of nivolumab or ipilimumab-related infusion reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4 guidelines.

Treatment of infusion reactions will follow Institutional standards.

8.2 Management Algorithms for Platinum-based Chemotherapy

Toxicities will be graded by using the NCI CTCAE version 4.0. Refer to the following website for the CTCAE manual or the CTCAE document:

http://ctep.cancer.gov

The dose modifications outlined below are considered general guidelines. The investigator should use his or her best judgment when determining treatment interruptions and dose

modifications. For example, some grade 2 non-hematologic toxicities may require treatment delays and/or dose reductions, and some grade 3 or 4 organ toxicities (e.g., hepatic, renal, cardiac, central nervous system) may require a permanent treatment discontinuation. If one chemotherapy agent (docetaxel/pemetrexed or cisplatin) needs to be discontinued/delayed, the other chemotherapy agent (cisplatin or docetaxel/pemetrexed) or nivolumab may be continued or delayed at the discretion of the treating physician. In the event that both cisplatin and docetaxel or cisplatin and pemetrexed need to be permanently discontinued, nivolumab will also be permanently discontinued. Docetaxel or pemetrexed or cisplatin doses will not be re-escalated once they have been reduced for toxicity.

8.2.1 Dose Modifications and Discontinuation Criteria of Platinum-based Chemotherapy

Dose reductions of platinum doublet regimens may be required and will be performed according to Table 8.2A below.

Table 8.2A: Dose Modifications for Platinum-Based Chemotherapy

Dose Level	Docetaxel	Pemetrexed	Cisplatin	Carboplatin
Starting dose	75 mg/m^2	500 mg/m²	75 mg/m²	AUC 5 or 6
First dose reduction	75% of starting dose	75% of starting dose	75% of starting dose	AUC 4 or 5
Second dose reduction	50% of starting dose	50% of starting dose	50% of starting dose	AUC 3 or 4
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue

Any participants with 2 prior dose reductions for 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Dose Modifications for Docetaxel

The dose of docetaxel will be reduced according to the following guidelines.

Thrombocytopenia

• If grade 4 thrombocytopenia occurs, the dose of docetaxel will be reduced by 1 dose level for subsequent cycles. If grade 4 thrombocytopenia persists despite two dose reductions, docetaxel treatment will be discontinued.

Neutropenia

The dose of docetaxel will be reduced for the following neutropenic conditions as outlined in Table 8.2B**:**
• Grade 4 neutropenia lasting ≥ 7 days

• Grade 3 or 4 febrile neutropenia

Table 8.2B: Docetaxel Dose Modifications for Neutropenia

Dose Description	Docetaxel Dose (mg/m^2)
starting dose	75 mg/m^2 (dose level 0)
1st dose reduction due to neutropenia (patients not receiving prophylactic growth factor support)	75 mg/m^2 (dose level 0) add growth factor support
1st dose reduction due to neutropenia (patients receiving prophylactic growth factor support)	75% of starting dose (dose level -1) continue growth factor support
2nd dose reduction due to neutropenia	50% of starting dose (dose level -2) continue growth factor support

If grade 4 neutropenia or grade 3-4 febrile neutropenia persists despite dose reduction to 50 mg/m2 (dose level -2) with growth factor support, docetaxel treatment will be discontinued.

Stomatitis

• If grade 3 or 4 stomatitis occurs, the dose of docetaxel will be reduced by one dose level for subsequent cycles. If grade 3 or 4 stomatitis persists despite two dose reductions, docetaxel treatment will be discontinued.

Peripheral Neuropathy

• If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy occurs, the dose of docetaxel will be reduced by one dose level. If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy persists despite two dose reductions, docetaxel treatment will be discontinued.

If grade 4 neuropathy occurs, docetaxel treatment will be discontinued.

Hypersensitivity Reactions

• There are no dose reductions for hypersensitivity reactions. Management of acute hypersensitivity reaction should follow the Institutional guidelines. Re-treatment with docetaxel will be allowed at the investigator's discretion.

• If grade 4 hypersensitivity reactions occur, docetaxel treatment will be discontinued.

Fluid Retention

• There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

Triamterene/hydrochlorothiazide one capsule (37.5 mg / 25 mg) po qd up to tid.

• Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.

• If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

Liver Enzyme Elevation

If liver enzyme elevations are considered to be related to docetaxel the algorithm in Table 8.2C below should be followed:

Table 8.2C: Docetaxel Dose Modification for Liver Enzyme Elevation:

Total Bilirubin		**Alkaline Phosphatase**		**SGOT or SGPT**	**Action**
> ULN	**OR**	> 5 x ULN	**OR**	> 5 x ULN	Delay treatment ≤3 weeks until recovery. If recovered*, reduce docetaxel dose by 25%. If not recovered in ≤3 weeks, discontinue docetaxel.

≤ ULN	**AND**	≤ 5 x ULN	**AND**	1.6 – 5 x ULN	Reduce docetaxel dose by 25%

*Bilirubin ≤ULN ***and*** alkaline phosphatase ≤5 x ULN ***and*** SGOT or SGPT ≤5 x ULN
Note: a maximum of two dose reductions per patient are allowed. If liver toxicities persist despite two dose reductions, docetaxel treatment will be discontinued.

Other Non-Hematologic Toxicities

If grade 3 or 4 clinically significant (as judged by the treating physician) non-hematologic toxicities occur (other than those listed above), docetaxel treatment will be withheld until the toxicity has resolved to ≤ grade 1 and then reinstituted (if medically appropriate) at the next lower dose level. If a grade 3 or 4 clinically significant toxicity recurs despite two dose reductions, docetaxel treatment will be discontinued.

If treatment is delayed for > 3 weeks due to a grade 3 or 4 toxicity, docetaxel treatment will be discontinued.

Dose Modifications for Cisplatin

The dose of cisplatin will be reduced according to the following guidelines.

Thrombocytopenia

If grade 4 thrombocytopenia occurs, the dose of cisplatin will be reduced by 1 dose level for subsequent cycles. If grade 4 thrombocytopenia persists despite two dose reductions, cisplatin treatment will be discontinued.

Neutropenia

The dose of cisplatin will be reduced for the following neutropenic conditions as outlined in Table 8.2D below**:**

• Grade 4 neutropenia lasting ≥ 7 days

• Grade 3 or 4 febrile neutropenia

Table 8.2D: Cisplatin Dose Modifications for Neutropenia

Dose Description	Cisplatin Dose (mg/m^2)
starting dose	75 mg/m^2 (dose level 0)
1st dose reduction due to neutropenia (patients not receiving prophylactic growth factor support)	75 mg/m^2 (dose level 0) add growth factor support
1st dose reduction due to neutropenia (patients receiving prophylactic growth factor support)	75% of starting dose (dose level -1) continue growth factor support
2nd dose reduction due to neutropenia	50% of starting dose (dose level -2) continue growth factor support

If grade 4 neutropenia or grade 3-4 febrile neutropenia persists despite dose reduction to 50 mg/m2 (dose level -2) with growth factor support, cisplatin treatment will be discontinued.

Other Non-Hematologic Toxicities

If any grade 3 or 4 toxicity occurs that is consistent with the cisplatin side effect profile (e.g., renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range [4000 to 8000 Hz], nausea and vomiting, hyperuricemia, moderate anemia, and irreversible peripheral neuropathy), the dose of cisplatin will be reduced by one dose level. If toxicities persist despite two dose reductions, cisplatin treatment will be discontinued.

Dose Modifications for Pemetrexed

Patients will be monitored closely for toxicity and the dose of pemetrexed may be adjusted as indicated in Table below. Pemetrexed dose reductions are permanent; once the dose is

reduced, it may not be re-escalated in subsequent cycles.
The dose of pemetrexed will be reduced for the following neutropenic conditions as outlined in Table 8.2E below**:**
• Grade 4 neutropenia lasting ≥ 7 days

• Grade 3 or 4 febrile neutropenia

Table 8.2E: Pemetrexed Dose Modifications for Neutropenia

Dose Description	Pemetrexed Dose (mg/m^2)
starting dose	500 mg/m^2 (dose level 0)
1st dose reduction due to neutropenia (patients not receiving prophylactic growth factor support)	500 mg/m^2 (dose level 0) add growth factor support
1st dose reduction due to neutropenia (patients receiving prophylactic growth factor support)	75% of starting dose (dose level -1) continue growth factor support
2nd dose reduction due to neutropenia	50% of starting dose (dose level -2) continue growth factor support

Thrombocytopenia

If grade 4 thrombocytopenia occurs, the dose of pemetrexed will be reduced by 1 dose level for subsequent cycles. If grade 4 thrombocytopenia persists despite two dose reductions, pemetrexed treatment will be discontinued.

Renal toxicity

Discontinue pemetrexed if creatinine clearance < 45 mL/min.

Other Non-Hematologic Toxicities

If any grade 3 or 4 toxicity occurs that is consistent with the pemetrexed side effect profile (e.g., fatigue, skin rash and/or desquamation and/or pruritus, increased ALT and AST, nausea

and vomiting, anorexia, stomatitis, diarrhea, moderate anemia, pharyngitis, edema, neuropathy, hypersensitivity reaction, conjunctivitis, constipation) the dose of pemetrexed will be reduced by one dose level. If toxicities persist despite two dose reductions, pemetrexed treatment will be discontinued.

Dose Modifications for Carboplatin

For the following hematologic toxicities the investigator must modify the carboplatin dose as detailed below:

Neutrophil Count Decreased Grade 4 (< 500/mm3 or < 0.5 x 109/L): Reduce one dose level and consider prophylactic GCSF in subsequent cycles
Platelet Count Decreased Grade 3 (25,000 to < 50,000/mm3; 25.0 to < 50.0 x 109/L): Reduce one dose Level
Platelet Count Decreased Grade 4 (< 25,000/mm3; < 25.0 x 109/L): Reduce one dose level
Hemoglobin decreased Grade 2 (< 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 - 80 g/L)**:** Reduce one dose level
Hemoglobin decreased Grade 3 (< 8.0 g/dL; < 4.9 mmol/L, < 80 g/L): Reduce one dose level
Hemoglobin decreased Grade 4 (Life-threatening consequences): Hold drug

For the following non-hematologic toxicities the investigator must modify the carboplatin dose as detailed below:
Febrile Neutropenia Grade ≥ 3 Reduce one dose level
Diarrhea Grade ≥ 3 No change
Allergic reaction[a] Grade ≥ 3 Discontinue
Neuropathy Grade 2 No change
Neuropathy Grade ≥ 3 Discontinue
Calculated creatinine clearance < 50 mL/min Discontinue if creatinine clearance < 20 mL/min
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia).

8.2.2 Re-treatment Criteria for Platinum-based Chemotherapy

Prior to receiving any dose of docetaxel or pemetrexed and cisplatin, patients must have an ANC ≥1.5 X 10^9/Land a platelet count ≥100 X 10^9/L; calculated creatinine clearance must be ≥45 mL/min or according to institutional standard practices for treatment with pemetrexed and cisplatin. If the ANC is < 1.5 X 10^9/L and platelet count is < 100 X 10^9/L, the treatment should be delayed for ≤ 3 weeks. If the patient is unable to be treated after a 3-week delay, the patient will be discontinued from chemotherapy. Patients who have temporarily discontinued chemotherapy will be allowed to continue on nivolumab, at the discretion of the treating physician.

8.2.3 Dose Delay Criteria for Platinum-based Chemotherapy

Dosing of both drugs in the platinum doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1.5 X 10^9 /L
- Platelets < 100 X 10^9 /L
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:

  Grade 3 lymphopenia does not require 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 which, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

If any non-hematologic adverse event meeting the dose delay criteria above is felt to be related to only 1 particular agent in the platinum doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met.

8.2.4 Discontinuation criteria for I-O agents

Treatment 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 adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis,

bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below

- 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 adverse event or laboratory abnormality, except for the following events which do not require discontinuation:

    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.

    - 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

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

    Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted

- Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing

If a patient discontinues treatment early, every attempt should be made to keep the patient in the study and perform the required End of Treatment assessments and Long-Term Follow-up Information.

NOTE: If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to nivolumab, ipilimumab or chemotherapy (if chemotherapy is part of the treatment regimen), the subject should discontinue nivolumab, ipilimumab and chemotherapy (if chemotherapy is part of the treatment regimen), and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study. The assessment for discontinuation of nivolumab and ipilimumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab and ipilimumab are met before the nivolumab and ipilimumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue to the discretion of the treating physician.

If the investigator is unable to determine whether an adverse event is due to nivolumab or ipilimumab or platinum doublet chemotherapy, then all drugs must be discontinued.

A subject who is discontinued from the chemotherapy treatment due to toxicities related to chemotherapy only, may remain on the study and receive nivolumab therapy only at the discretion of the treating physician.

If any adverse event meeting the dose delay criteria for chemotherapy is felt to be related to only one particular agent in the platinum doublet chemotherapy regimen, then that chemotherapy agent alone may be omitted for that cycle while the other agents are given. Dosing of nivolumab and both chemotherapy agents should be delayed if criteria for nivolumab or “both platinum-doublet chemotherapy agents” are met.

Concomitant Medication(s) During Platinum-Based Chemotherapy

Anticancer therapy with agents other than cisplatin/pemetrexed or cisplatin/docetaxel and I-O agents is not allowed. Medications intended solely for supportive care (ie, anti-emetics, analgesics, megestrol acetate for anorexia) are allowed. NSAIDs with long half-lives, eg, >10 hours, should be discontinued at least 5 days before, the day of and 2 days following pemetrexed dosing. Patients who take NSAIDs concomitantly with pemetrexed should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicity.

9 STUDY ASSESSMENTS AND PROCEDURES

Baseline evaluation:

Investigations		Timing
History and Physical Exam including:	• Treatment history • Vital signs • Medical history • ECOG PS • Smoking history • TNM stage • Height and weight	Within 14 days prior to treatment initiation
Current Smoking Status and Tobacco Use	• Assessment of patient's current smoking status and tobacco use	Within 14 days prior to randomization
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0	Within 14 days prior to treatment initiation
Concomitant Medications	• Documentation of concomitant medications	Within 14 days prior to treatment initiation
Hematology and Coagulation	• CBC with hemoglobin, platelets, and WBC with differential • Prothrombin time (PT) / Partial thromboplastin time (PTT)	Within 14 days prior to treatment initiation
Biochemistry	• Albumin • Glucose • Alkaline phosphatase • LDH • Potassium • Total bilirubin, direct, indirect • SGOT (AST) • SGPT (ALT) • BUN • Sodium • Creatinine • Magnesium • Total protein • Uric acid • Free T4, TSH	Within 14 days prior to treatment initiation
Pregnancy Test	• Urine or serum (for women of childbearing potential only)	Within 48 hours prior to treatment initiation

Radiology	• CT chest	Within 30 days prior to treatment initiation
Radiology	• PET-CT	Within 60 days prior to treatment initiation
Radiology	• MRI brain or CT brain (only for patients with stage II or III on pre-operative staging)	Within 60 days prior to treatment initiation
Mediastinal staging	• CT chest / PET-CT, mediastinoscopy, and/or endobronchial ultrasound	Within 60 days prior to treatment initiation
Pulmonary tests	• Complete pulmonary function test[2] • 6-Minute Walk Test[3]	Prior to treatment initiation
Tumor Tissue Collection for Biomarkers	• Archival tissue or new biopsy of primary tumor for biomarker analysis (optional) • Tissue obtained for mediastinal staging (optional)	Prior to treatment initiation
Blood-based biomarkers	• Blood sample	Prior to treatment initiation
Stool-based Microbiome	• Stool sample	Prior to treatment initiation

[1] If information / studies have already been obtained but chemotherapy is delayed for any reason, repeated studies are not necessary prior to next cycle of chemotherapy.
[2]Complete pulmonary function test may not be required if patient is no longer considered a surgical candidate post immunotherapy plus chemotherapy based on the treating physician's discretion.
[3] This test is encouraged and not mandatory. Before the 6MWT: The patient should rest for at least 15 minutes before beginning the 6MWT. Record: Blood pressure, Heart rate, Oxygen saturation (SpO_2), Respiratory rate At the End of the 6MWT: Put a marker on the distance walked, Seat the patient or, if the patient prefers, allow to the patient to stand, Immediately record oxygen saturation (SpO2)%, heart rate and respiratory rate.

Evaluation during neoadjuvant treatment (prior to each nivolumab single agent infusion- ARM A and B):

Investigations			Timing
Physical Exam Including:	• BSA • Vital signs		Within 7 days prior to dose #2 and #3 of nivolumab
Hematology	• CBC with hemoglobin, platelets, and WBC with differential		Within 7 days prior to dose #2 and #3 of nivolumab
Biochemistry[1]	• Albumin • Alkaline phosphatase • Total bilirubin, direct, indirect • BUN • Creatinine • Total protein • Free T4, TSH	• Glucose • LDH • Potassium • SGOT (AST) • SGPT (ALT) • Sodium • Magnesium • Uric acid	Within 7 days prior to dose #2 and #3 of nivolumab
Radiology [1]	• CT chest • PET-CT		At least 14 days after the last dose of immunotherapy
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0		On an ongoing basis throughout the study until the final study visit

Concomitant Medications	• Documentation of concomitant medications	On an ongoing basis throughout the study until the final study visit
Blood-based biomarkers[1]	• Blood sample	Within 7 days prior to dose #2 and #3 of nivolumab and at least 14 days after the last dose of immunotherapy
Pulmonary tests	• Complete pulmonary function test[2]	At least 14 days after the last dose of immunotherapy
Stool-based Microbiome	• Stool sample	At least 14 days after the last dose of immunotherapy
[1] If information / studies have already been obtained but chemotherapy is delayed for any reason, repeated studies are not necessary prior to next cycle of chemotherapy. [2]Complete pulmonary function test may not be required if patient is no longer considered a surgical candidate post immunotherapy based on the treating physician's discretion.		

Evaluation during neoadjuvant treatment (prior to each I-O agent/s plus platinum-based chemotherapy infusion- ARM C and ARM D):

Investigations		Timing
Physical Exam Including:	• BSA • Vital signs	Within 7 days prior to cycles 2- 3, and at least 14 days after the last cycle of chemotherapy and immunotherapy
Hematology	• CBC with hemoglobin, platelets, and WBC with differential	Within 7 days prior to cycles 2-3, and at least 14 days after the last cycle of chemotherapy and immunotherapy

Biochemistry[1]	• Albumin • Alkaline phosphatase • Total bilirubin, direct, indirect • BUN • Creatinine • Total protein • Free T4, TSH	• Glucose • LDH • Potassium • SGOT (AST) • SGPT (ALT) • Sodium • Magnesium • Uric acid	Within 7 days prior to cycles 2-3, and at least 14 days after the last cycle of chemotherapy and immunotherapy
Radiology [1]	• CT chest • PET-CT		At least 14 days after the last cycle of chemotherapy and immunotherapy
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0		On an ongoing basis throughout the study until the final study visit
Concomitant Medications	• Documentation of concomitant medications		On an ongoing basis throughout the study until the final study visit
Blood-based biomarkers[1]	• Blood sample		Within 7 days prior to cycle #2 and #3 of chemotherapy and nivolumab and at least 14 days after the last dose of immunotherapy
Pulmonary tests	• Complete pulmonary function test[2] • 6-Minute Walk Test[3]		At least 14 days after the last dose of chemotherapy and immunotherapy

Stool-based Microbiome	• Stool sample	At least 14 days after the last dose of chemotherapy and immunotherapy

[1] If information / studies have already been obtained but chemotherapy is delayed for any reason, repeated studies are not necessary prior to next cycle of chemotherapy.
[2]Complete pulmonary function test may not be required if patient is no longer considered a surgical candidate post immunotherapy plus chemotherapy based on the treating physician's discretion.
[3] This test is encouraged and not mandatory. Before the 6MWT: The patient should rest for at least 15 minutes before beginning the 6MWT. Record: Blood pressure, Heart rate, Oxygen saturation (SpO_2), Respiratory rate At the End of the 6MWT: Put a marker on the distance walked, Seat the patient or, if the patient prefers, allow to the patient to stand, Immediately record oxygen saturation (SpO2)%, heart rate and respiratory rate.

Assessments at surgery:

Investigations		Timing
Surgical procedure	• Title of operation • Status of resection margins (R0, R1, R2)	Through chart review
	• pTNM • Major pathologic response • Percentage of viable tumor cells • Nodal stations dissected / sampled and nodal status (positive vs. negative) at each station • Evaluation of extra-capsular nodal spread	

End of treatment assessments:

Investigations		Timing
Physical Exam	• Vital Signs	Approximately within 8 weeks after surgery
Blood-based biomarkers	• Blood sample	Approximately within 8 weeks after surgery
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0 • Retrospective evaluation of any	Approximately within 8 weeks after surgery

Long-term follow-up

After the End of Treatment evaluation, information on additional oncologic treatment (including post-operative systemic therapy and radiation therapy), time to disease progression/recurrence, sites of recurrence, development of second primary tumors, additional therapy for recurrence, long-term survival, and other relevant clinical data will be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

Long-term follow up will be conducted as long as needed to obtain relevant information for accurate interpretation of the study. No pre-specified time frame is defined.

9.1 Description of Study Assessments

9.1.1 Performance status

The performance status of all patients will be graded according to the ECOG PS scale.

9.1.2 Clinical laboratory tests

Clinical laboratory tests will be performed to assess eligibility for enrolment and will be repeated according to Tables included in this section.

Laboratory tests can be repeated more frequently, if clinically indicated.

9.1.3 Symptoms and toxicity assessment

The symptoms and adverse events of all patients will be graded at scheduled intervals according to the NCI CTCAE, v4.0. Patients will be monitored continuously throughout the study for the occurrence of adverse events. Planned medical interventions (e.g., planned surgical resection) will not be considered an adverse event. For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported. Unexpected surgical complications will be retrospectively reviewed at the end of treatment assessments.

9.1.4 Radiology assessments

CT chest, PET-CT, and CT brain / MRI brain will be obtained according to Tables included in this section. CT chest examinations maybe obtained with dual energy modality.

Response and progression will be evaluated in the study using the international criteria proposed by the RECIST committee,[30] and preferably by the same investigator or collaborator.

Patients enrolled to this study may also be offered optional participation in a separate IRB-approved protocol evaluating additional imaging modalities for NSCLC. An independent informed consent process will be followed for accrual to such protocol.

9.1.5 Mediastinal staging

Mediastinal staging should be accomplished by obtaining at least a CT chest or PET-CT. It is recommended that patients with suspicious mediastinal lymph node involvement by PET-CT and/or CT chest undergo a mediastinoscopy or endobronchial ultrasound with biopsies for more detailed mediastinal staging. It is also strongly recommended that patients with clinical N1 disease and/or central tumors undergo mediastinoscopy or endobronchial ultrasound with

biopsies. Patients with clinical N0 disease and a peripheral lesion may not warrant mediastinoscopy or endobronchial ultrasound with biopsies.

9.1.6 Tumor tissue samples

Archival tissue samples will be collected for histopathological examination and biomarkers, when available (at least 20 unstained slides and/or a tissue block are preferred). A new baseline tumor tissue sample from the primary tumor may be collected for histopathological examination and biomarkers. Samples will be obtained by an outpatient image-guided biopsy procedure (preferably core biopsy) or bronchoscopy. These specimens should be fixed in 10% formalin, preferably immediately and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. A portion of the specimen obtained (or a second biopsy) will also be embedded in optimal cutting temperature compound and/or RNA later and/or culture media immediately after received and not more than 1 (one) hour after excision, frozen, and processed and/or stored at -80 ^{O}C for future biomarker analysis. All samples stored at -80 ^{O}C should be placed in appropriate containers, labeled with the protocol number and the patient's unique study identification number.

Tissue obtained during mediastinal staging may also be collected for biomarker evaluation.

Tumor tissue will also be obtained at surgical resection. The recommended procedure for obtaining the tissue specimens is as follows: a portion of the resected tumor tissue will be fixed in 10% formalin immediately after received and not more than 1 (one) hour after excision. Fixed samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. Another portion of the tumor specimen (preferably at least one sample ≥ 2 mm^3 or 100 mg) will be embedded in optimal cutting temperature compound and/or RNA later and/or culture media immediately after received and not more than 1 (one) hour after excision, frozen and processed and/or stored at -80 ^{O}C for biomarker analysis. The freshly collected tumor tissues with or without adjacent lung tissue samples placed in culture media immediately after received will be processed for single cell suspension for single cell genomics (37). Each cell will be bar-coded using 10x genomics technology (or other equivalent technologies) and libraries (RNA, DNA, or epigenomics) for sequencing. The sequenced data will be analyzed and we plan to associate sequencing data with clinical parameters. The

remaining specimens resected during surgery will be used for routine histopathological diagnosis and will also be stored for future biomarker studies. Normal lung tissue uninvolved by tumor and/or normal lymph node tissue uninvolved by tumor may also be collected and processed / stored as above, for biomarker evaluation.

The surgical specimens will be evaluated for pathologic staging (pTNM) according to the AJCC 7th edition, pathologic complete response, quantification of percentage of viable tumor cells, status of resection margins, number of lymph nodes removed at each level, number of lymph nodes positive for cancer at each level, presence of extra-capsular nodal spread. To determine the pathologic response, specimens will be grossed and processed by the thoracic pathologist. The entire specimen measurement and the size of visible residual tumor will be documented. At least 1 block/1 cm of tumor will be submitted (average of 5-10 blocks/patient). All slides prepared from blocks taken from each specimen will be reviewed by the thoracic pathologist, as well as slides from each dissected lymph node.

Sample sharing: In some cases samples may be sent to or received from outside collaborators such as Broad Institute for next-generation sequencing and/or analysis. All samples will be sent under a specific contract or Material Transfer Agreement (MTA). We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

Internal/External Sequencing may be done here at MD Anderson, in one of the Core labs such as Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as Broad Institute. Sequencing performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA).

Data Sharing: Researchers can do more powerful studies when they share with each other the information they get from studying human samples. NGS data may be placed in a local M.D. Anderson Institutional Data Repository, commonly referred to as BigData; where both deposition of and access to data require governance and approval. In some cases, grant requirements may require deposition of large-scale data into the public Genotypes and Phenotypes database (dbGaP) an access controlled database overseen by the National Center for Biotechnology Information (NCBI). In other cases peer reviewed Journals may require

data to be shared through a resource such as dbGaP. Data submitted to those repositories will only be shared in a de-identified fashion and without associated clinical data or identifiers. This data will be used only for research purposes, and the data elements collected and analyzed will only be those that are necessary to conduct this research.

Database access additional protections: The precedent to publically broadcast sequence data has been set by large consortial projects, such as The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE), in order to maximize data utility. However, we know there is the potential for privacy risks associated with the release of sequence data to databases and while the risk may be small it could grow in the future as technology advances. To minimize this potential, we will implement good faith efforts to ensure patient confidentiality and reduce patient exposure. The database of Genotypes and Phenotypes and others like it are extremely access restricted. Only authorized researchers may deposit or access the data and either or both efforts require MD Anderson institutional approval. Sequence data will only be broadcast through secure transmission processes. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees. Only non-identifiable data will be deposited to dbGaP i.e., no linking table or access to a linking table will be available. Research records will be kept separate from medical records and patients will not have access to any of the research data.

Protected health information (PHI) may be collected from medical records that are related to health and/or disease history including test results, medical procedures, and images (such as X-rays) in addition demographic and environmental factors may be requested. Researchers will use this information to better understand how genes affect health and response to treatment. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees.

9.1.7 Blood-based biomarkers

Blood will be collected (60 mL), at scheduled intervals according to Tables 9-1 to 9-5 for plasma and blood cells separation and storage. Samples from the main campus will be forwarded to the core laboratory to be processed. Samples from the Regional Care Centers (Katy, Sugarland, Bay Area, and Woodlands) will be collected and placed in ice-bags for delivery to the core laboratory preferably by 3 PM on the day it is collected.

9.1.8 Stool-based biomarkers

Patients will provide their stool samples as detailed in the tables above. Stool collection will

be performed with commercially available collection kits from DNA Genotek company. These kits will be provided to patients at no cost.

9.1.9 CT imaging-based biomarkers

The imaging data will be saved to retrospectively reconstruct and post-process the images for further investigating advanced quantitative algorithms with the goal to improve detection and characterization of disease along with potential biomarkers to assess response to immune checkpoint blockade.

9.1.10 Long-term follow-up

After the End of Treatment evaluation, information on additional oncologic treatment (including post-operative systemic therapy and radiation therapy), time to disease progression/recurrence, sites of recurrence, development of second primary tumors, additional therapy for recurrence, long-term survival, and other relevant clinical data will be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

9.1.11 Assessments for premature discontinuation from study

If a patient discontinues treatment early, every attempt should be made to keep the patient in the study and perform the required End of Treatment assessments and to obtain Long-Term Follow-up Information.

10 TISSUE AND BLOOD SAMPLE REPOSITORY

As part of the study, a tissue and blood sample repository will be created. The objective of this tissue sample repository will be to provide material for the correlative studies proposed to evaluate the endpoints proposed (including primary, secondary, exploratory endpoints and additional assessments previously described in this protocol), and for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. A written informed consent will be obtained from patients enrolled in this study so that these samples may be analyzed in the future for biomarkers not described in this protocol.

11 ADVERSE EVENT COLLECTION AND REPORTING

All Serious Adverse Events (SAEs) that occur upon the subject's first protocol specific intervention on this study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

11.1 Definitions

11.1.1 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 subject administered an investigational (medicinal) product 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 investigational product, whether or not considered related to the investigational product.

For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported.

Attribution or the causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest causal relationship. There are three attributions listed for related to investigational agent/intervention:

- Possible- The AE ***may be related*** to the intervention
- Probable-The AE ***is likely related*** to the intervention
- Definite- The AE ***is clearly related*** to the intervention

Not related (unrelated): There is not a reasonable causal relationship between study drug administration and the AE. There are two attributions listed for unrelated to investigational agent or intervention:

- Unrelated-The AE is clearly ***NOT*** related to the intervention
- Unlikely-The AE is ***doubtfully related*** to the intervention

Adverse events that will be captured in this study consist of:

- adverse events grades 3, 4, and 5 regardless of relationship or attribution
- adverse events grades 1 and 2 that are possibly, probably or definitely related to treatment

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

11.1.2 Serious adverse events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Potential drug induced liver injury (DILI) is also considered an important medical event.

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

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 72 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).

11.2 Serious Adverse Event and Pregnancy Reporting

11.2.1 Serious Adverse Event Reporting

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

SAEs, whether related or not related to study drug, must be reported to BMS within 24 hours. SAEs must be recorded on BMS ***approved form***.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

The **principal 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 principal investigator. The principal 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

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to Worldwide.Safety@BMS.com.

SAEs will be reported on the BMS approved form for prompt reporting (full form):

"Internal SAE Report Form for Prompt Reporting" Institutional Review Board.

SAEs will be submitted to both the Office of Protocol Research, Unit 1437 at The University of Texas MD Anderson Cancer Center and also sent to:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to:

BMS at: Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb
Company Fax Number:
609- 818-3804
Email: Worldwide.safety@bms.com

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new

information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.2.2 Pregnancy and Reporting

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

investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures within 24 hours.

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 [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form

11.2.3 Potential Drug Induced Liver Injury

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. Potential drug induced liver injury is defined as:

1) 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 AST/ALT 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.

11.2.4 Non-serious adverse events

Non-serious Adverse Events are to be provided to BMS in aggregate via interim or final study

reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.

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

Non-serious adverse events will be captured as defined in section 11.1.1 from initiation of the study drug until the end of treatment assessment (as defined by the schedule in section 9), or to resolution or stabilization, whichever is longer.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

11.3 Laboratory test abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events (or serious adverse events) if they meet the definition of an adverse event (or serious adverse event).

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE

- any laboratory abnormality that required the subject to have study drug discontinued or interrupted

- any laboratory abnormality that required the subject to receive specific corrective therapy.

11.4 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.

11.5 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

12 RECORDING AND COLLECTION OF DATA

12.1 Case Report Forms

Clinical data capture called DMI (Data Management Initiative) will be the electronic database used for this study's electronic case report forms.

Use of concomitant medications is routinely captured in the patient's electronic medical record and the information is readily available if it needs to be obtained for analysis of study results. As such, concomitant medications will not be captured in the Protocol's database.

13. Sample and Data Sharing

Samples and data collected during this study will be shared with internal and external collaborators for the purposes of meetings study related objectives. Data/Samples are being shared with institutional and external and for tissue/data analyses described in this protocol, including the International Association for The Study of Lung Cancer (IASLC); the University of Pittsburg and the Yale School of Medicine/Yale Cancer Center.

14 STATISTICAL CONSIDERATIONS

In this multi single arm phase II study, eligible patients will be accrued to the nivolumab alone arm (Arm A), the nivolumab plus ipilimumab arm (Arm B), the nivolumab plus platinum-based chemotherapy arm (Arm C) or nivolumab plus ipilimumab plus platinum-based chemotherapy (Arm D). The primary efficacy endpoint of the study is the major pathologic response in resected tumor tissues following neoadjuvant therapy, as compared to the MPR induced by neoadjuvant chemotherapy in historical controls. Patients that do not undergo surgery will be considered as treatment failure for the major pathologic response analysis. At the end of the trial, if the primary efficacy endpoints demonstrate significant findings, further evaluation of the immune- based neoadjuvant therapy in NSCLC will be warranted.

Time-to-event endpoints will be computed using the Kaplan-Meier method.

Multivariate analysis will be used to explore the role of biomarkers in predicting pathologic response to treatment, in an exploratory way.

By performing WES in blood germline genetic alterations may be detected. As a consequence, patients will be contacted and informed and a genetic consult will be placed and or recommended for possible retesting.

Sample size calculation is based on the assumptions described below.

Primary endpoint of major pathologic response:

- The study is a multi -arm phase II trial with modular design and this primary endpoint will be compared to the pre-specified major pathologic response target based on the historical data.

- The historic major pathologic response rate to neoadjuvant chemotherapy alone is 19% (as described by Pataer et al.) (20). However, some patients that receive neoadjuvant chemotherapy may not receive surgery for one reason or another, and these cases will be considered treatment failure. Assuming the 19% major pathologic response rate is calculated from 80% of patients who receive surgery, a conservative estimate of the major pathologic response is 15%. Preliminary results from a small scale phase 2 study evaluating the safety and feasibility of neoadjuvant nivolumab for early stage NSCLC patients indicate that nivolumab is safe and neither delays surgery nor induces surgical complications when given preoperatively (19). Indeed, neoadjuvant nivolumab induces major pathologic response in 45% (9/20) of

patients (19), which is markedly increased relative to the one noted following neoadjuvant chemotherapy (19%) (20). Our goal is to determine if nivolumab alone or nivolumab plus ipilimumab, or nivolumab plus platinum-based chemotherapy, or nivolumab plus ipilimumab plus platinum-based chemotherapy can produce a major pathologic response which is better than 15% (i.e., immunotherapy would be at least as effective as chemotherapy, the major pathologic response rate under the null hypothesis) with a target a major pathologic response rate of 40% (i.e., the target major pathologic response rate).

- Simon's minimax two-stage design (38) will be applied to test the major pathologic response rate for each one of the treatment arms. We assume the 15% major pathologic response rate under the null hypothesis versus the 40% major pathologic response rate under the alternative hypothesis. For each treatment arm, 15 patients will be enrolled in the first stage. If only two or less of the 15 patients have major pathologic response, enrollment to that treatment arm will be terminated and the treatment is considered inefficacious. Otherwise, with at least three major pathologic responses, additional 6 patients will be enrolled to reach a total of 21 patients. At the end of trial, if we observe 6 or more patients have major pathologic response, the treatment is considered efficacious and inefficacious otherwise. The trial will have 90% power when the major pathologic response rate is 40%. When the major pathologic response rate is 15%, the probability of early termination is 0.60 with an average sample size of 17.4 and one-sided 10% type I error rate. With 21 patients and assuming the major pathologic response rate is at 0.40, we can estimate the major pathologic response rate with a standard error of 0.107.

- We will also apply the Bayesian framework to calculate the posterior probability of major pathologic response rate. The 95% credible interval of the major pathologic response rate will be constructed. In addition, we will calculate the probability that the major pathologic response rate is at least 15% under the beta-binomial model. Assume that the prior distribution of the major pathologic response rate is Beta (0.15, 0.85). With 6 responses in 21 patients, we will be 92.9% confident to conclude that the major pathologic response rate for the treatment is at least 15%.

From the above calculations, the study will need up to 21 evaluable patients in each arm. Assuming a non-evaluable rate of 5% (e.g., patients drop out, lost to follow-up, or rescind the consent due to non-treatment related reasons before endpoints can be evaluated), we will need to enroll up to a total of 88 patients (total 22 patients per arm with up to 21 evaluable patients in each arm). With an estimated accrual rate of 2-3 patients a month, the accrual period is approximately 35 months.

Analysis of Secondary Objectives/Endpoints:

Analysis for the secondary objectives and/or secondary endpoints will be descriptive and exploratory in nature. Descriptive statistics will be provided to summarize the data distribution. Association analysis by Pearson or Spearman correlation coefficient will be calculated for continuous data and chi-square or Fisher's exact test for categorical data. The goals for these analyses are for hypothesis generating. The results will need to be confirmed by future studies.

15 STUDYMONITORING AND EARLY STOPPING RULES

The study will be monitored by the MD Anderson Data Safety and Monitoring Board.

To ensure the safety of the proposed treatment in the neoadjuvant setting, precautions have been taken into consideration and implemented:

- A careful review of the literature has demonstrated that the use of neoadjuvant chemotherapy does not increase surgical morbidity or mortality (12). Because single agent nivolumab has been found to have a more favorable adverse event profile than single agent chemotherapy (17, 18) it is expected that neoadjuvant immunotherapy will be feasible and safe.
- A Bayesian method to monitor the toxicity in the perioperative phase will be used. Unacceptable toxicity is defined as: severe pneumonitis precluding performance of planned surgical resection, death during neoadjuvant treatment or within 30 days after surgery; severe post op acute respiratory distress syndrome (ARDS) not attributable to aspiration requiring prolonged ventilator support; development of broncho-pleural fistula not attributable to surgical technique; wound healing delays that require management with a major surgical procedure; wound infections that require intravenous antibiotic use for more than 21 days; re-operation for bleeding or infection deemed secondary other factors than surgical technique; empyema; stroke or myocardial infarction within 30 days after surgery; any treatment-related adverse events leading to a delay in surgery resulting in > 8 week interval between the last dose of nivolumab and surgery, any surgical complication that is considered major by the treating physician and possibly, probably or definitely related the immunotherapy medications. The incidence of surgical complications for thoracoscopy/thoracotomy for non-small cell lung cancers is approximately 16-31% (39). We consider that a neoadjuvant therapy with one of the regimens is not feasible if it results in unacceptable toxicities in at least 30% of the patients with 70% or higher probability.

  With a prior probability of toxicity as Beta (0.5,0.5), the toxicity stopping boundaries are defined as seeing unacceptable toxicity in >= 3 of 6-7, 4 of 8-10, 5 of 11-13, 6 of 14-16, 7 of 17-19, or 8 of 22 patients. When the true toxicity rates are 0.1, 0.3, and 0.5, the probabilities of early stopping are 0.03, 0.54, and 0.96 with the corresponding average sample sizes of 21.5, 14.8, and 7.9, respectively. In case one arm needs to be closed due to excessive toxicity, accrual to the remaining arm will continue in a non-

randomized way. The calculation was performed using the Shiny Application: Bayesian Toxicity Monitoring version 2.1 (http://ibl.mdanderson.org/BTM/)

In case one arm needs to be discontinued at completion of stage I due to lack of efficacy, according to the Simon's two stage design described above, accrual to the other arms will continue.

The Investigator is responsible for completing the efficacy/safety summary report and submitting it to the IND office Medical Monitor for review and approval. These should be submitted as follows:

For Safety Monitoring:

After the first 6 evaluable patients per arm, reach 30 days post-surgery, after the first 8, and every 3 consecutive evaluable patients per arm, thereafter. On every report submission, the toxicity information from previous reported patients will need to be updated.

For Efficacy Monitoring:

After the first 15 evaluable patients per arm, reach 30 days after surgery, and after all evaluable subjects per arm, complete 30 days post-surgery.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

16 APPENDICES

Appendix 1 Sample of Drug Ordering and Pharmacy Reference Material

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab and ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.*

- *The initial order should be limited to the amount needed for two doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.*

- *Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In- line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*

- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

Please refer to the most recent version of the nivolumab and ipilimumab Investigator Brochure for additional information to be included as per institutional or regulatory standards.

Nivolumab (BMS-936558) Pharmacy Reference Material

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration

Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.

- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab.

  Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.

- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

Use Time/Stability:

Please refer to the appropriate section of the current Investigator Brochure or Addendum. Due to parameters surrounding the use time of nivolumab and ipilimumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP]

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558- 01 injection in the IV bag includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles. *Note: Mix by gently inverting several times. Do not shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*
4. ***Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]***
5. *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.*

6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.

7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Ipilimumab Pharmacy Reference Material

Ipilimumab vials (40 mL) are shipped in quantities of four.

Ipilimumab (BMS-734016) Injection (5 mg/ml) must be stored refrigerated (2-8°C, 36-46°F) with protection from light and from freezing. Ipilimumab may be stored in IV infusion bags (PVC, non- PVC/non-DEHP) or glass infusion containers for up to 24 hours at room temperature (20-25°C, 68-77°F) or refrigerated (2-8°C, 36-46°F). This would include any time in transit and the total time for infusion. Drug must be completely delivered within 24 hours of preparation.

Storage Conditions & Handling:

Ipilimumab injection may be stored undiluted, 200 mg/vial (5 mg/mL), or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours in the refrigerator (2°C to 8°C) or at room temperature/room light. For longer storage, ipilimumab should be kept refrigerated (2 C to 8 C) with protection from light. Ipilimumab injection must not be frozen.

Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

Preparation and Administration

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration.

1. As ipilimumab is stored long term at refrigerated temperatures (2-8ºC) and protected from light, allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.

2. Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
3. Aseptically transfer the required volume of ipilimumab solution into a syringe. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
4. Do not draw into each vial more than once. Discard partially used vials or empty vials.

5. Ipilimumab solution should be added to an appropriate size infusion container to accommodate the calculated final volume.
   Total dose should be calculated using the most recent subject weight; if weight on dosing day differs by 10% from prior weight used to calculate dosing, the dose should be recalculated and study drug adjusted accordingly.
   Mix by GENTLY inverting several times. DO NOT shake.

   Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

6. Visually inspect the final solution. If the initial diluted solution or final solution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
7. Immediately after the infusion is complete, flush with an adequate amount of 0.9% Sodium Chloride injection (USP) or 5% Dextrose injection (USP) to completely flush the residual fluid (dead space) in your administration set (approximately 30-50mL); this will ensure that all active drug is delivered to the study participant
8. Safely discard any unused portion of the infusion solution. Do not store for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. <u>It is imperative that only product designated for this protocol be</u> <u>used for</u>

Appendix 2 Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno- oncology 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.

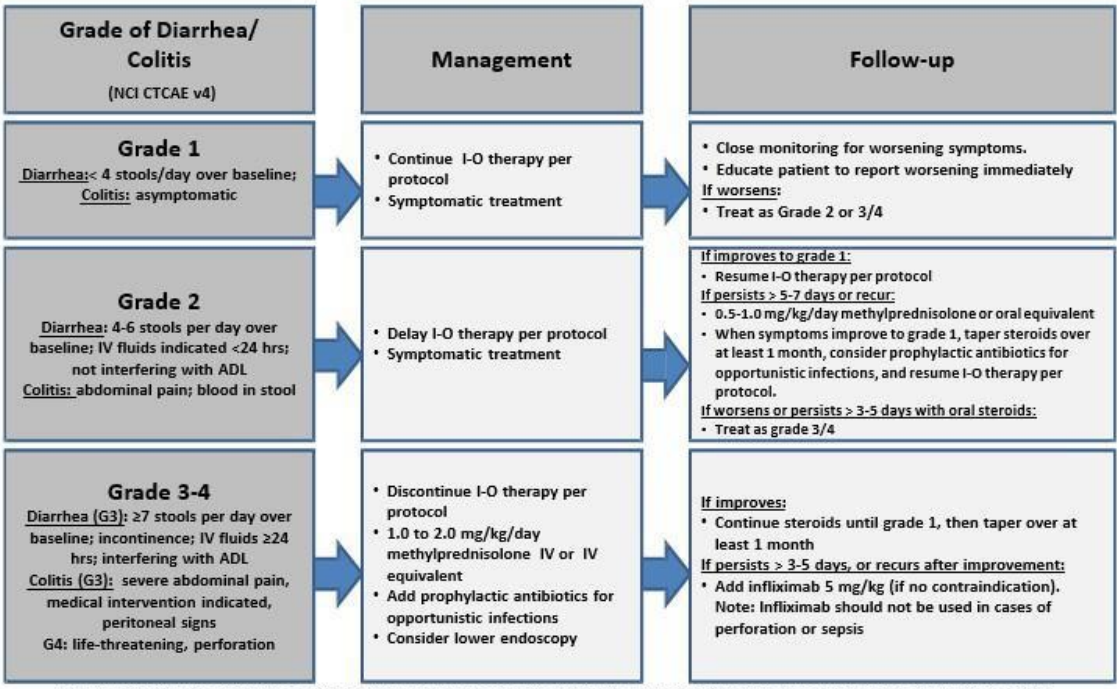
Corticosteroids are a primary therapy for immuno-oncology drug- related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the 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.

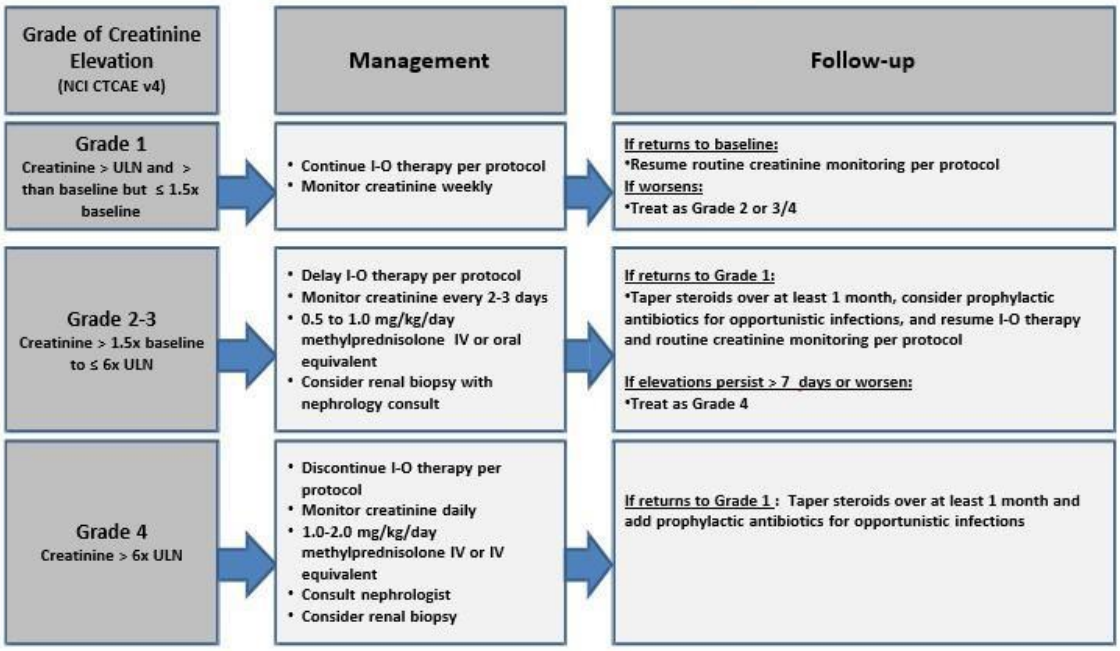


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

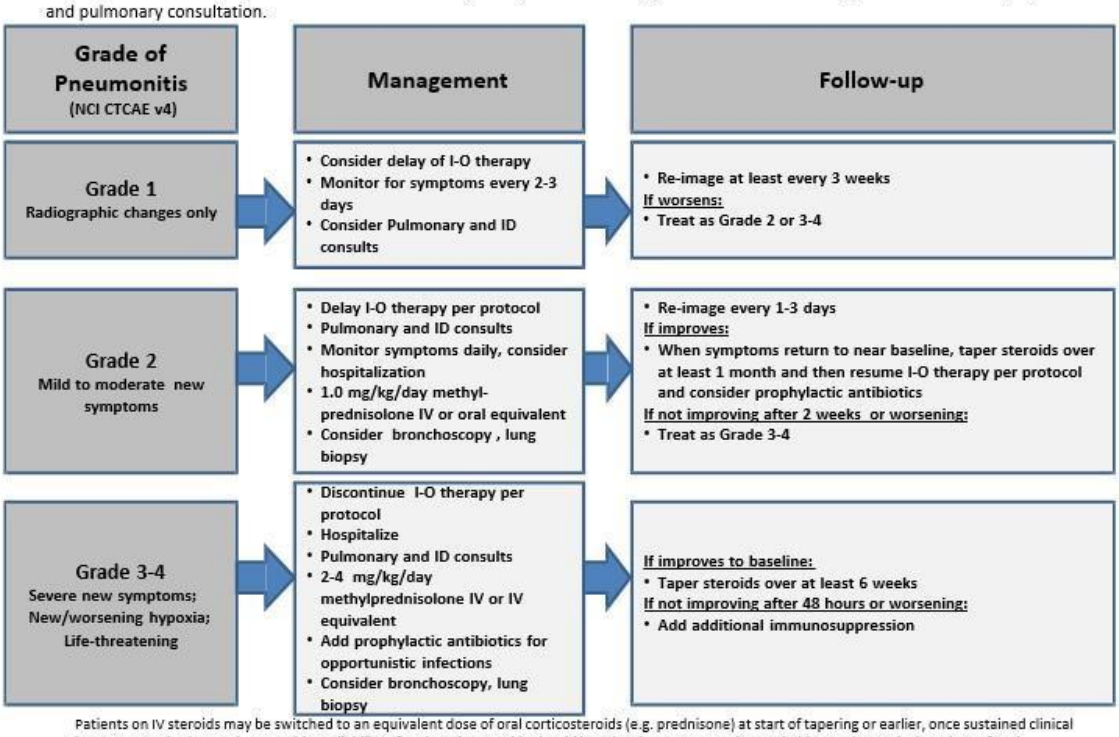


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

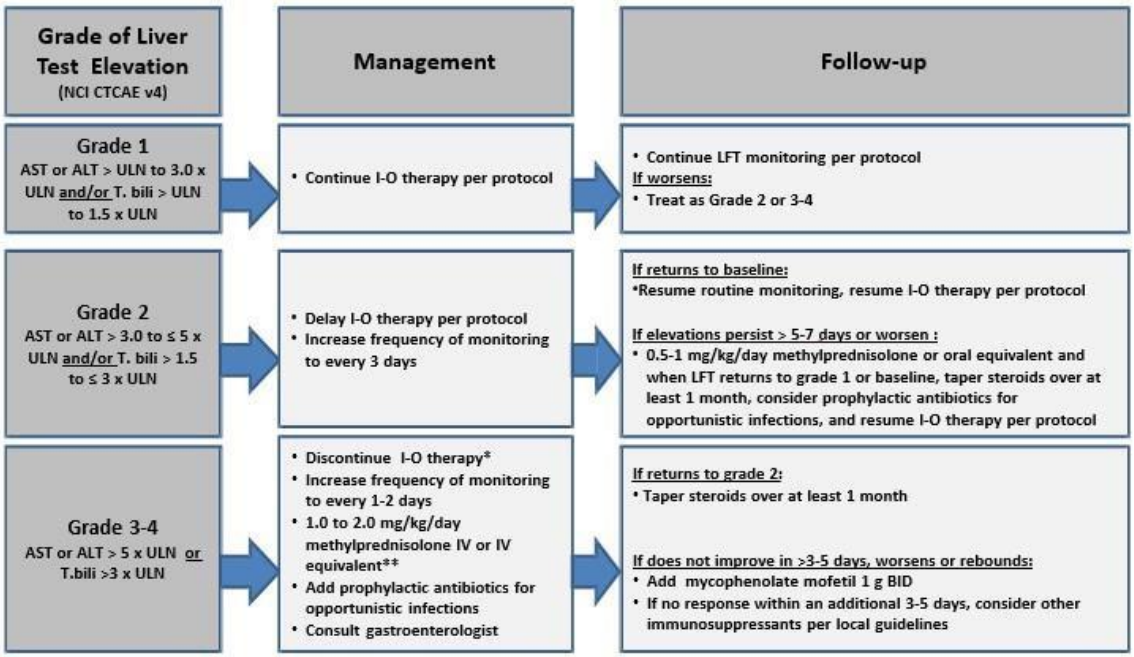


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

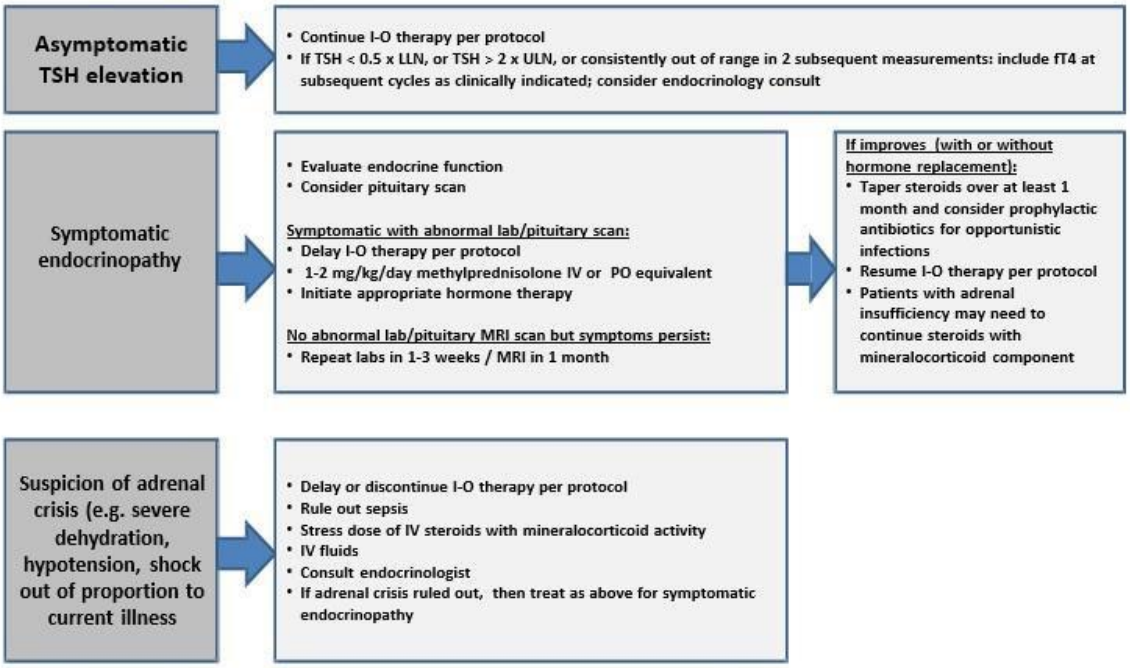
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**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.

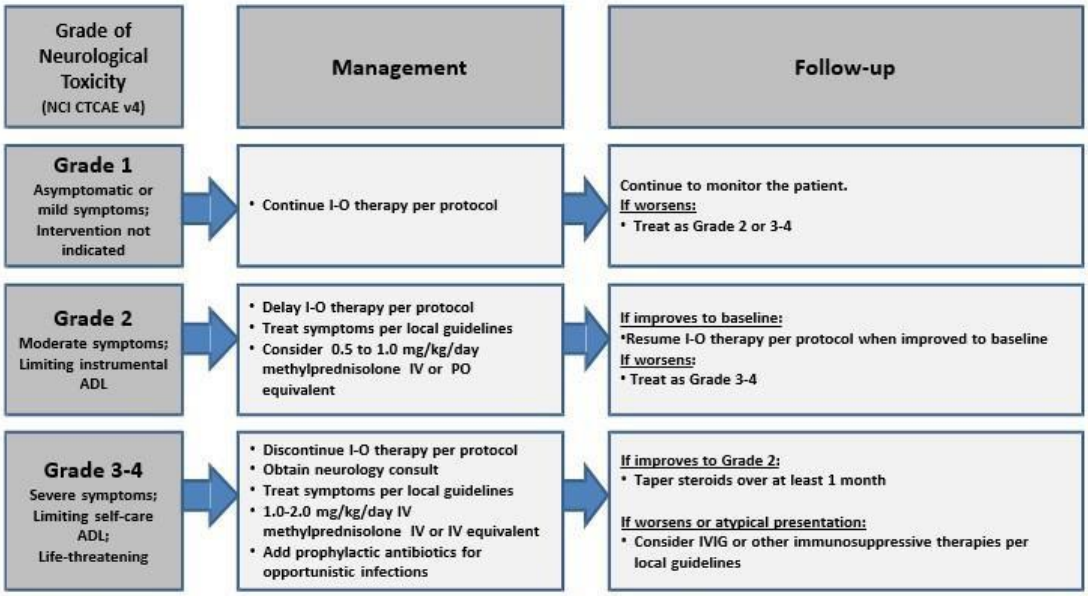


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Neurological 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

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